SOME BETA-HYDROXYPROPYL SULFIDES AND THEIR DERIVATIVES

By

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PREFACE

Since this dissertation is concerned primarily with the synthesis of compounds new to the literature, the material relative to the synthesis of these compounds is given in detailed form for all products as an aid to further investigation, even though essentially the same basic procedure may be followed in the synthesis of compounds of a homologous series.

All temperatures are based on the centigrade scale and its symbol is, therefore, omitted.

Melting and boiling points given are corrected values, the thermometers used in obtaining these values having been calibrated against a set of thermometers standardized by the United States Bureau of Standards.

References are given in the manner usual for technical reports of this sort. Journal abbreviations are those standardized upon by "Chemical Abstracts".

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INTRODUCTION

Though the preparation of epoxy compounds and the reactions of these compounds with substances containing active hydrogen have been known for nearly one hundred years, only in relatively recent times have studies been conducted on the specific reaction between alkene oxides and mercaptans. The dearth of material on this subject, as well as a desire to extend the work of Flores-Gallardo (1) on epoxy ethers to epoxy sulfides, initiated this investigation.

The purpose of the investigation was primarily to:

1. Synthesize chlorohydroxysulfides through the interaction of epichlorohydrin and mercaptans;

2. Synthesize epoxysulfides a) from chlorohydroxysulfides and sodium hydroxide and/or b) from epichlorohydrin and alkali mercaptides;

3. Synthesize hydroxydisulfides a) from epoxysulfides and mercaptans, b) from chlorohydroxysulfides and alkali mercaptides, and/or c) from epichlorohydrin with an equimolar alkali mercaptide- mercaptan mixture;

4. Synthesize chlorohydroxysulfones through the oxidation of chlorohydroxysulfides;

5. Synthesize epoxysulfones from chlorohydroxysulfones and sodium hydroxide;

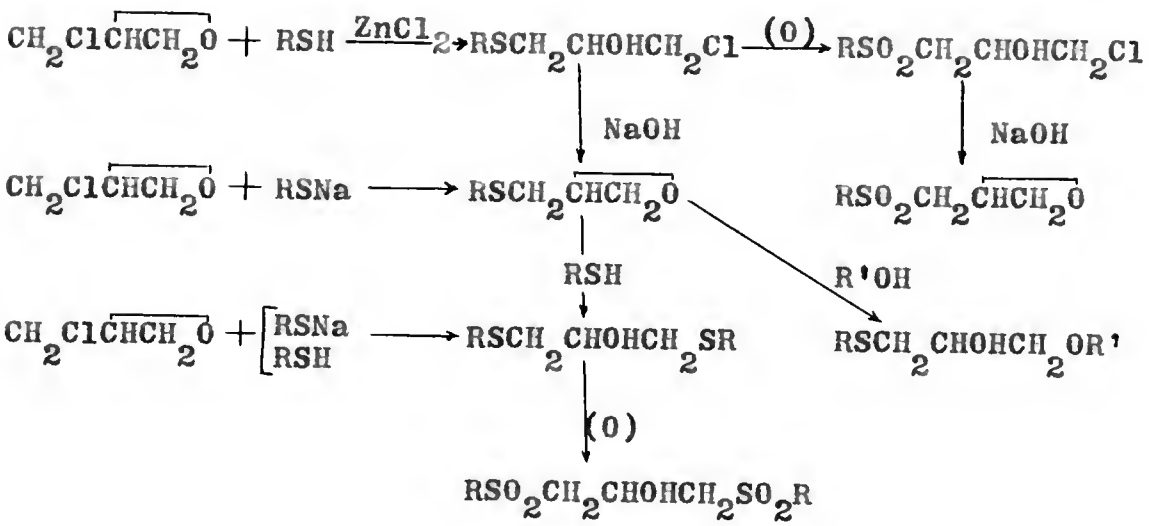
6. Synthesize hydroxydisulfones by oxidation of

hydroxydisulfides;

7. Synthesize alkylthiohydroxy ethers from epoxysulfides and alcohols;

8. Investigate the course of the reactions outlined in 1 and 3 above through proof of the structure of the products obtained in each.

The reactions through which the above syntheses are carried out may be diagrammed as follows:



DISCUSSION AND EXPERIMENTAL

A. Synthesis of chlorohydroxypropyl sulfides

1. Review of the literature

Studies concerned with the reaction of epoxides with hydrogen sulfide or mercaptans are met with only in relatively recent literature, the first being in 1935 when Chichibabin and Bestuzhev (2) investigated the reaction between ethylene oxide and hydrogen sulfide. In the same year, Nenitzescu and Scarlatescu (3) conducted a much more extensive study, involving the reaction of ethylene oxide, cyclohexene oxide, and epichlorohydrin with hydrogen sulfide, ethyl mercaptan, propyl mercaptan, thiophenol, and benzyl mercaptan. The reaction of these mercaptans with epichlorohydrin, either with or without an activated charcoal catalyst, produced chlorohydroxypropyl sulfides in 90% yields, this being the first reported preparation of these compounds.

Sjöberg (4) reported the reaction of epichlorohydrin with hydrogen sulfide in alkaline solution to give 1-mercapto-3-chloro-2-propanol. Tseou and Pau (5) investigated the high temperature interaction of ethylene oxide and hydrogen sulfide, in the presence of a catalyst. The Shell Development Company (6) obtained 1-pentylthio-3-chloro-2-propanol by the method of Nenitzescu and Scarlatescu (3).

By treating 1,3-dichloro-2-propanol with sodium ethyl

mercaptide or sodium benzyl mercaptide in aqueous alcohol, Rothstein (7) synthesized 1-ethylthio-3-chloro-2-propanol and 1-benzylthio-3-chloro-2-propanol. It is probable that, in this reaction, the first step is a dehydrohalogenation of the 1,3-dichloro-2-propanol to epichlorohydrin, which then reacts with the mercaptan present to give the end product. This follows from the work of Fairbourne, Gibson, and Stephens (8) who showed that this is the mode of addition of alcohols to 1,3-dichloro-2-propanol in the presence of a base.

2. Experimental

a. Synthesis of 1-methylthio-3-chloro-2-propanol

One mole (48 g.) of methyl mercaptan, one mole (92 g.) of epichlorohydrin, one gram of anhydrous zinc chloride, and 150 ml. of dioxane were placed in a 500 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser, and refluxed for three hours. Low boiling material (dioxane and unreacted mercaptan and epichlorohydrin) was removed under aspirator vacuum at a maximum temperature of 70°, using a water bath as a source of heat. The residue was then distilled at 1.4 mm., 1-methylthio-3-chloro-2-propanol being collected at 55°.

B.P. : 55° at 1.4 mm.

Yield : 56 g., 0.4 mole, 40%

n_D^{25} : 1.5094

d_4^{25} : 1.2250

M_D : 34.30 (found); 35.03 (calc.)

% C : 34.28 (found); 34.16 (calc.)

% H : 6.25 (found); 6.45 (calc.)

b. Synthesis of 1-ethylthio-3-chloro-2-propanol

0.8 mole (50g.) of ethyl mercaptan and 0.5 mole (46 g.) of epichlorohydrin were placed in a 200 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. The well stirred mixture was heated and on reaching reflux, one gram of zinc chloride was added through the condenser. The mixture was heated for an additional five minutes to initiate the reaction. At this point the heat of reaction necessitated cooling. After the reaction ceased, heating was resumed for one hour. The excess ethyl mercaptan was removed under aspirator vacuum and the residue was distilled at 1.5 mm, 1-ethylthio-3-chloro-2-propanol being collected at 68-69°.

B.P. : 68-69° at 1.5 mm.

Yield : 57 g., 0.37 mole, 74%

n_D^{25} : 1.5047

d_4^{25} : 1.1651

M_D : 39.36 (found); 39.66 (calc.)

% C : 38.80 (found); 38.83 (calc.)

% H : 7.53 (found); 7.17 (calc.)

c. Synthesis of 1-propylthio-3-chloro-2-propanol

0.6 mole (45 g.) of propyl mercaptan and 0.5 mole (46 g.) of epichlorohydrin were placed in a 200 ml., three-necked, round-bottomed flask, equipped with stirrer, thermometer, and reflux condenser. The mixture was heated to reflux and one gram of zinc chloride was added through the reflux condenser. After five minutes, a vigorous reaction occurred which was controlled by strong cooling. After completion of the reaction, the mixture was heated to the former reflux temperature (84°) for thirty minutes, cooled and distilled at 1.4 mm., 1-propylthio-3-chloro-2-propanol being obtained at 79-80°.

B.P. : 79-80° at 1.4 mm.

Yield : 61 g., 0.36 moles, 73%

n_D^{25} : 1.4986

d_4^{25} : 1.1286

M_D : 43.92 (found); 44.28 (calc.)

% C : 42.46 (found); 42.79 (calc.)

% H : 7.76 (found); 7.76 (calc.)

d. Synthesis of 1-butylthio-3-chloro-2-propanol

0.56 mole (50 g.) of butyl mercaptan and 0.5 mole (46 g.) of epichlorohydrin were placed in a 200 ml., three-necked, round-bottomed flask, equipped with stirrer, thermometer, and reflux condenser. The mixture was heated to reflux with vigorous stirring and one gram of zinc chloride

was added through the reflux condenser. After three minutes, a vigorous exothermic reaction necessitated strong cooling. The cooled mixture was again heated to the former reflux temperature for thirty minutes. It was then distilled at 0.5 mm., 1-butylthio-3-chloro-2-propanol being collected at 76-77°.

B.P. : 76-77° at 0.5 mm.

Yield : 57 g., 0.32 mole, 64%

n_D^{25} : 1.4940

d_4^{25} : 1.0883

M_D : 48.86 (found); 48.90 (calc.)

% C : 45.74 (found); 46.01 (calc.)

% H : 8.35 (found); 8.28 (calc.)

e. Synthesis of 1-pentylthio-3-chloro-2-propanol

0.5 mole (52 g.) of pentyl mercaptan and 0.5 mole (46 g.) of epichlorohydrin were placed in a 200 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. The stirred mixture was heated to reflux and one gram of zinc chloride was added through the condenser. The resulting vigorous reaction necessitated external cooling, and when this reaction had subsided the mixture was heated to the former reflux temperature for thirty minutes. It was then distilled at 0.5 mm., 1-pentylthio-3-chloro-2-propanol being collected at 85-86°.

B.P. : 85-86° at 0.5 mm.

Yield : 45 g., 0.23 mole, 46%

n_D^{25} : 1.4900

d_4^{25} : 1.0664

M_D : 53.34 (found); 53.51 (calc.)

% C : 48.82 (found); 48.84 (calc.)

% H : 8.84 (found); 8.71 (calc.)

f. Synthesis of 1-hexylthio-3-chloro-2-propanol

0.55 mole (65 g.) of hexyl mercaptan and 0.5 mole (46 g.) of epichlorohydrin were placed in a 200 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. The mixture was heated to reflux with stirring and one gram of zinc chloride was added through the condenser. After subsidence of the strongly exothermic reaction, the mixture was reheated to the original reflux temperature for thirty minutes, then distilled at 0.5 mm., 1-hexylthio-3-chloro-2-propanol being obtained at 96-97°.

B.P. : 96-97° at 0.5 mm.

Yield : 78 g., 0.37 mole, 74%

n_D^{25} : 1.4880

d_4^{25} : 1.0465

M_D : 58.02 (found); 58.14 (calc.)

% C : 50.92 (found); 51.28 (calc.)

% H : 9.21 (found); 9.09 (calc.)

3. Discussion of experimental results

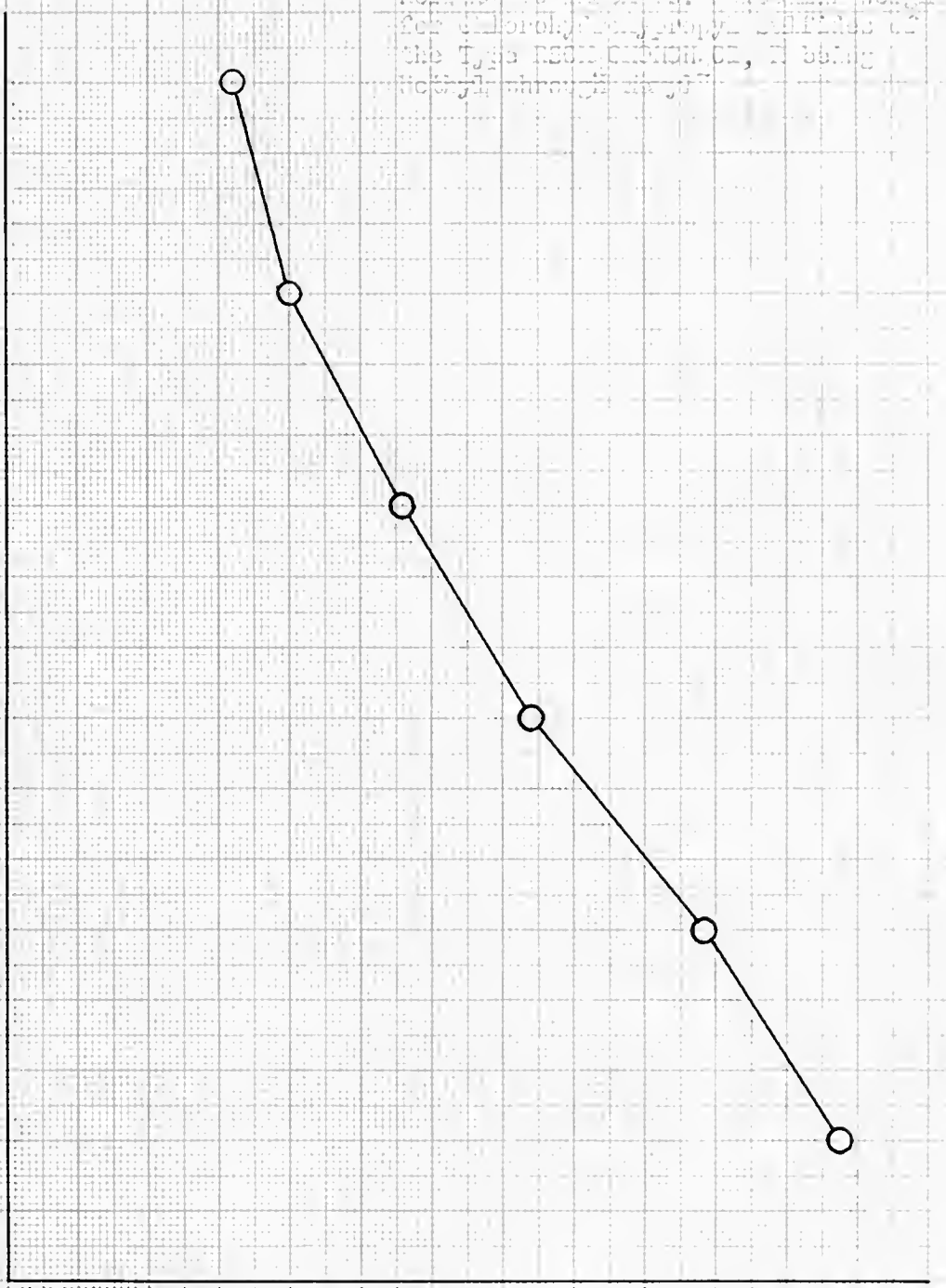
Figures 1, 2, and 3 show the variation in densities, refractive indices, and molecular refractions of the chlorohydroxypropyl sulfides with molecular weights.

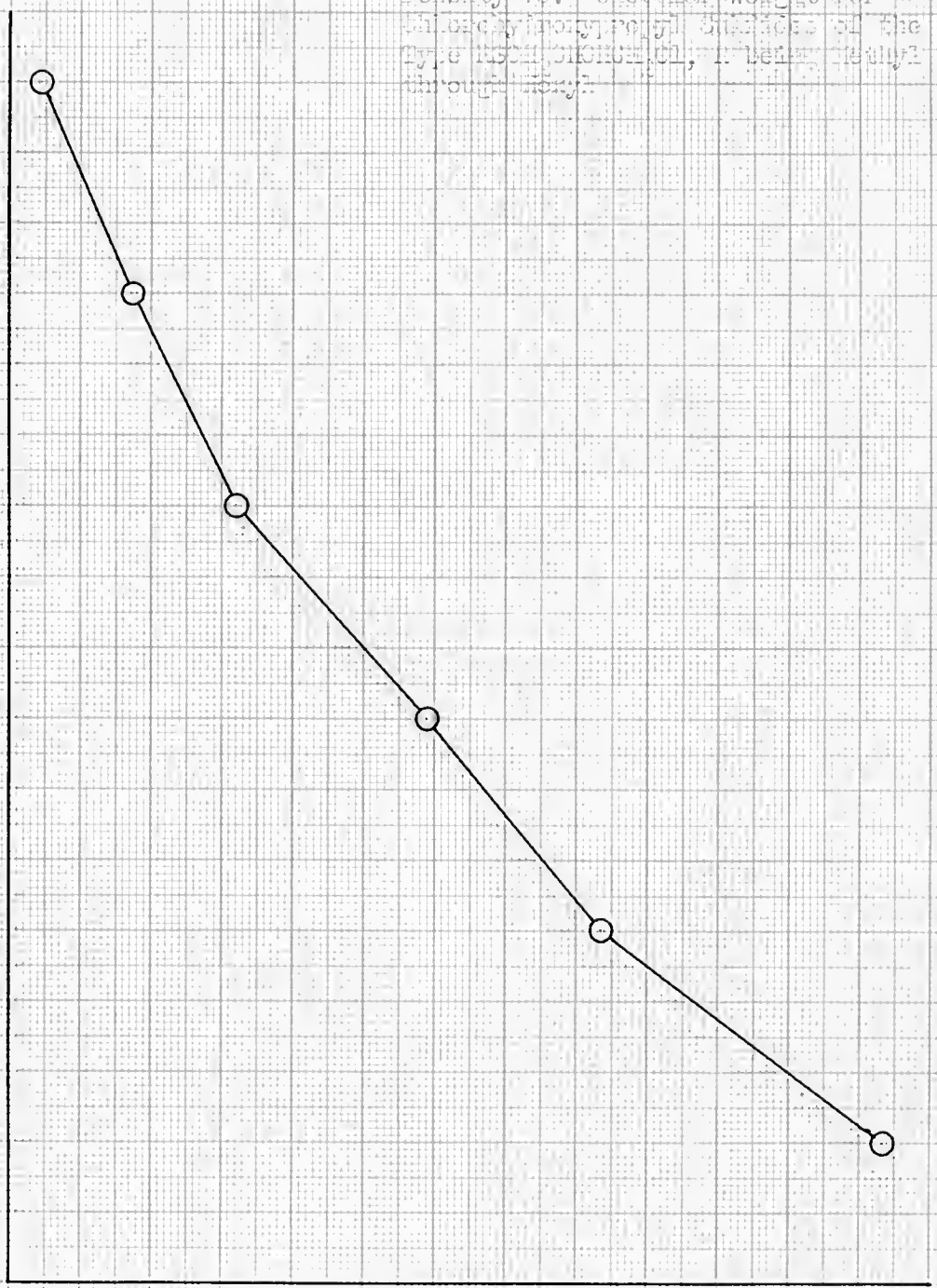
In this portion of the investigation, an attempt was made to synthesize 1-ethylthio- and 1-propylthio-3-chloro-2-propanols by the method of Nenitzescu and Scarlatescu (3). The results were entirely negative, almost complete recovery of the initial reactants being effected in each case. Use of sulfuric acid as a catalyst according to the procedures of Flores- Gallardo and Pollard (1) and Swern, Billen, and Knight (9) resulted in a yield of 44%. Zinc chloride proved to be the best catalyst, reducing the reaction time from a minimum of four hours to thirty minutes and providing yields of about 70%.

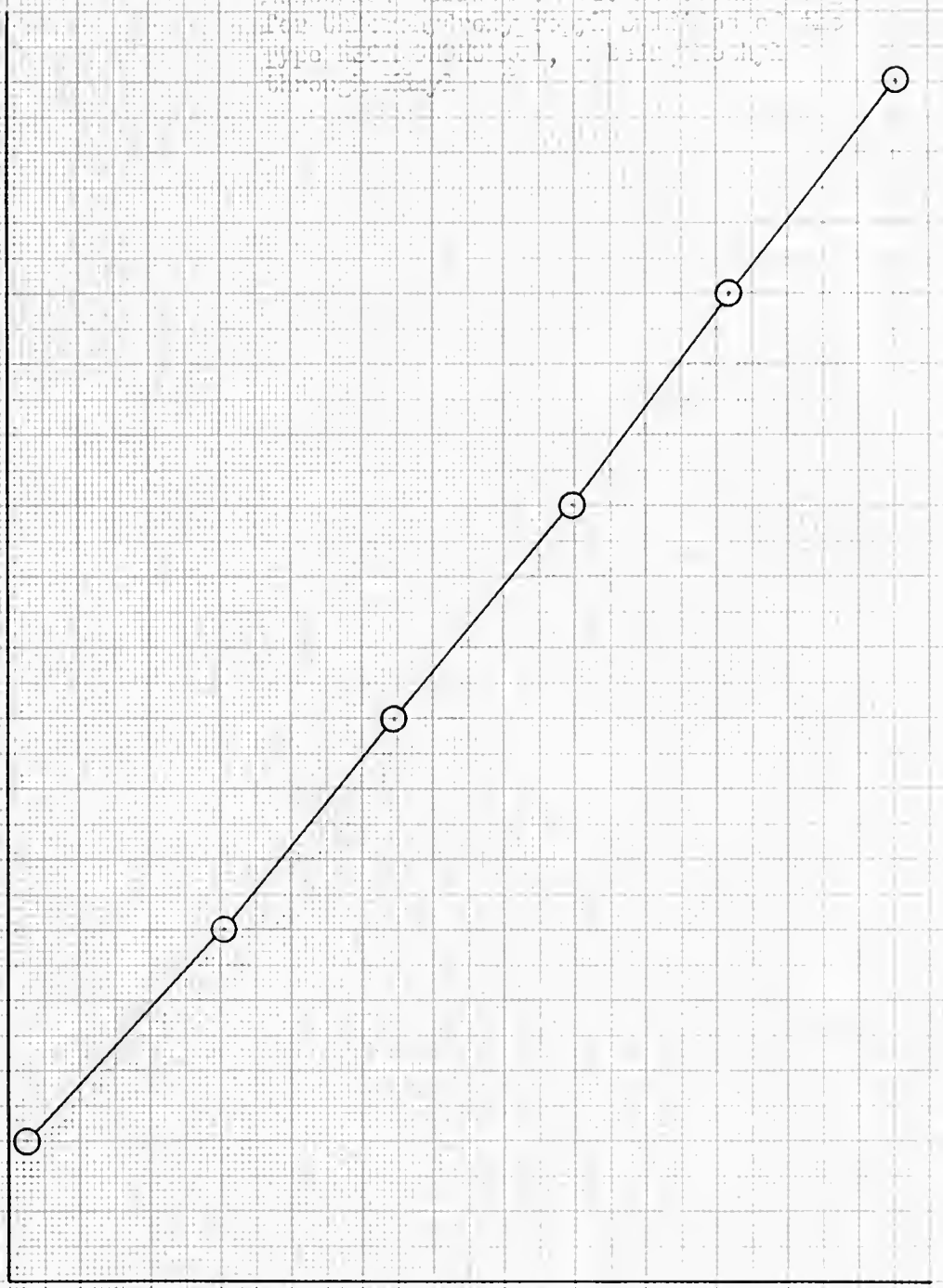
The method outlined was satisfactory for the preparation of all except the methyl derivative. The reaction with methyl mercaptan leads to a highly viscous polymerized material, probably through the formation of sulfonium linkages which are much more easily formed in methyl sulfides. It was necessary, in this instance, to carry out the reaction in an inert solvent.

4. Summary

A new method for the preparation of alkylthiochloropropanols is described. Individual syntheses for methyl,







ethyl, propyl, butyl, amyl, and hexyl derivatives are described, of which methyl, butyl, and hexyl are newly reported compounds. The boiling points of the ethyl and propyl derivatives are the only physical constants previously reported in the literature.

B. Synthesis of epoxypropyl sulfides

1. Review of the literature

Epoxides have been prepared in many ways. Epichlorohydrin or epibromohydrin were made by Berthelot and Luca (10) as one of the products of the reaction of phosphorus trichloride or phosphorus tribromide on glycerol. Dehydrohalogenation of a 1,2 chlorohydrin by alkali hydroxides in various solvents is an old and well known process for the preparation of these compounds (1), (8), (11), (12), (13), (14), (15). More recently, oxidation of a double bond, either by perbenzoic acid (16), (17) or by air in the presence of appropriate catalysts (18), (19) has come into prominence as a preparative method for oxiranes.

The synthesis of epoxysulfides has been carried out by dehydrohalogenation and by a modified Williamson synthesis. Nenitzescu and Scarlatescu (3) produced 1-ethylthio-2,3-epoxypropane by dehydrohalogenation of 1-ethylthio-3-chloro-2-propanol with aqueous sodium hydroxide and by treatment of epichlorohydrin with an aqueous solution of sodium ethyl mercaptide. The Shell Development Company (6) reported the

synthesis of 1-pentylthio-2,3-epoxypropane by dehydrohalogenation. Gilman and Woods (20) treated epichlorohydrin in anhydrous alcohol with mercaptides of the type $(CH_3)_2NCH_2(CH_2)_nCH_2SNa$ to obtain epoxysulfides.

2. Experimental

a. Synthesis of 1-methylthio-2,3-epoxypropane

Two moles (190 g.) of epichlorohydrin was placed in a one l., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. The flask was cooled in an ice-salt mixture and a freshly prepared ice-cold potassium methyl mercaptide solution (prepared by dropwise addition of 2.1 moles (100 g.) of methyl mercaptan to a cooled stirred solution of 2.1 moles (137 g.) of 85% KOH in 150 ml. of water) was added dropwise with vigorous stirring. The stirring was continued for two hours after the addition was completed. The layers that formed were separated and the aqueous layer extracted twice with ethyl ether. The ethereal extracts and the non-aqueous layer were combined, dried over anhydrous calcium sulfate, and distilled at 70 mm. 1-methylthio-2,3-epoxypropane was obtained at 84.5-85°.

B.P. : 84.5-85° at 70 mm.

Yield* : 39.5 g., 0.38 mole, 19%

n_D^{25} : 1.4817

* This preparation yielded both this product and 1,3-bis(methylthio)-2-propanol.

d_4^{25} : 1.0583

M_D : 28.04 (found); 28.34 (calc.)

% C : 45.52 (found); 46.12 (calc.)

% H : 8.07 (found); 7.74 (calc.)

b. Synthesis of 1-ethylthio-2,3-epoxypropane

(1) A solution of 19 grams of 85% potassium hydroxide in 40 ml. of water was placed in a 200 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and dropping funnel. To the vigorously stirred, cooled solution was added dropwise 0.11 mole (17 g.) of 1-ethylthio-3-chloro-2-propanol. After stirring for two hours following addition of the chlorohydroxysulfide, the mixture was extracted twice with ethyl ether, the combined extracts dried over anhydrous calcium sulfate, and the dried ethereal solution distilled; 7 grams (54%) of 1-ethylthio-2,3-epoxypropane was obtained.

(2) A solution of two moles (82 g.) of sodium hydroxide in 300 ml. of water was placed in a one l., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. The flask was cooled in ice slush and two moles (124 g.) of ethyl mercaptan added dropwise. The resulting sodium ethyl mercaptide solution was added dropwise with vigorous stirring to two moles (185 g.) of epichlorohydrin contained in a similarly equipped flask. After addition of the mercaptide solution, the mixture was stirred for two hours.

The layers of the mixture were separated, the aqueous layer extracted twice with ethyl ether, and the extracts and non-aqueous layer combined and dried over anhydrous potassium carbonate. The dried solution was distilled, 1-ethylthio-2, 3-epoxypropane being collected at 3.5 mm.

B.P. : 41.5-42° at 3.5 mm.

Yield : 163 g., 1.38 moles, 69%

n_D^{25} : 1.4757

d_4^{25} : 1.0170

M_D : 32.76 (found); 32.96 (calc.)

% C : 50.73 (found); 50.81 (calc.)

% H : 8.77 (found); 8.53 (calc.)

c. Synthesis of 1-propylthio-2,3-epoxypropane

0.33 mole (31 g.) of epichlorohydrin was placed in a 200 ml., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. To the cooled, vigorously stirred epichlorohydrin was added dropwise a solution of potassium propyl mercaptide (prepared from 24 grams of 85% potassium hydroxide and 25 grams of propyl mercaptan). Stirring was continued for two hours after the addition was completed. The two layers formed were separated, the aqueous layer extracted twice with ethyl ether, and the extracts and the non-aqueous layer combined. The resulting solution was dried over anhydrous calcium sulfate, filtered, and distilled, 1-propylthio-2,3-epoxypropane being collected at 43-44° at 2 mm.

B.P. : 43-44° at 2 mm.

Yield : 25 g., 0.19 mole, 57%

n_D^{25} : 1.4730

d_4^{25} : 0.9905

M_D : 37.44 (found); 37.58 (calc.)

% C : 54.66 (found); 54.50 (calc.)

% H : 9.59 (found); 9.15 (calc.)

d. Synthesis of 1-butylthio-2,3-epoxypropane

0.23 mole (43 g.) of 1-butylthio-3-chloro-2-propanol and 400 ml. of ethyl ether were placed in a one l., three-necked, round-bottomed flask, equipped with stirrer and reflux condenser. 40 grams of powdered sodium hydroxide was slowly added to the vigorously stirred, cooled solution. Stirring was continued for twelve hours. The mixture was then filtered and dried over anhydrous calcium sulfate. The dried solution was filtered, the ethyl ether removed under reduced pressure, and the residue distilled at 70 mm., 1-butylthio-2,3-epoxypropane being obtained at 132-132.5°.

B.P. : 132-132.5° at 70 mm.

Yield : 17 g., 0.12 mole, 50%

n_D^{25} : 1.4723

d_4^{25} : 0.9716

M_D : 42.17 (found); 42.20 (calc.)

% C : 57.72 (found); 57.49 (calc.)

% H : 10.14 (found); 9.65 (calc.)

e. Synthesis of 1-pentylthio-2,3-epoxypropane

0.33 mole (31 g.) of epichlorohydrin was placed in a 200 ml., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. A potassium pentyl mercaptide solution was prepared by dropwise addition of 0.33 mole (35 g.) of pentyl mercaptan to a cooled, stirred solution of 0.33 mole (24 g.) of potassium hydroxide in 100 ml. of 95% ethanol. This mercaptide solution was added dropwise to the cooled, stirred epichlorohydrin. Stirring was continued for six hours. The resulting mixture was extracted three times with ethyl ether and the combined extracts dried over anhydrous potassium carbonate. The dried, filtered solution was distilled, 1-pentylthio-2,3-epoxypropane being obtained at 67-68° at 1.6 mm.

B.P. : 67-68° at 1.6 mm.

Yield : 27 g., 0.17 mole, 50%

n_D^{25} : 1.4707

d_4^{25} : 0.9544

M_D : 46.90 (found); 46.82 (calc.)

% C : 59.92 (found); 59.95 (calc.)

% H : 10.26 (found); 10.06 (calc.)

f. Synthesis of 1-hexylthio-2,3-epoxypropane

0.33 mole (31 g.) of epichlorohydrin was placed in a 200 ml., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. A potass-

ium hexyl mercaptide solution was prepared by dropwise addition of 0.33 mole (40 g.) of hexyl mercaptan to a cooled, stirred solution of 0.33 mole (24 g.) of 85% potassium hydroxide in 100 ml. of 95% ethanol. The mercaptide solution was added dropwise to the cooled, stirred epichlorohydrin. Stirring was continued for six hours. The resulting mixture was extracted three times with ethyl ether and the combined extracts dried over anhydrous potassium carbonate. The dried, filtered solution was distilled, 1-hexylthio-2,3-epoxypropane being collected at 69.5-70° at 0.7 mm.

B.P.	:	69.5-70° at 0.7 mm.
Yield	:	17.5 g., 0.11 mole, 32%
n_D^{25}	:	1.4702
d_4^{25}	:	0.9471
M_D	:	51.36 (found); 51.44 (calc.)
% C	:	62.00 (found); 62.01 (calc.)
% H	:	10.64 (found); 10.41 (calc.)

3. Discussion of experimental results

The method of Nenitzescu and Scarlatescu (3) for the preparation of epoxysulfides from chlorohydroxysulfides was repeated with fair results. It is felt that dehydrohalogenation according to the modification of Flores-Gallardo and Pollard (1) is somewhat more advantageous since the product of the initial reaction with alkali is an essentially dry, ethereal solution of the desired epoxysulfide and is much easier to handle.

The method of Nenitzescu and Scarlatescu (3) which involves the reaction of epichlorohydrin and an aqueous solution of an alkali mercaptide included the dropwise addition of epichlorohydrin to the cold sodium mercaptide solution. Repetition of this preparation led to very poor yields. It was supposed that, in the presence of the excess of mercaptide, the epichlorohydrin reacted completely to form bis (alkylthio) propanols. When the order of addition was reversed, i.e., when the mercaptide solution was added dropwise to epichlorohydrin, there was an excess of epichlorohydrin present at all times, so that good yields were obtained.

In the calculation of the molecular refractions of these epoxysulfides, the value for the atomic refraction of epoxy oxygen used was 1.890, as determined by Flores-Gallardo and Pollard (1).

Figures 4, 5, and 6 show the variation in refractive index, density, and molecular refraction for these compounds as their molecular weight varies.

It may be seen that, generally, yields were of the same order, whether a chlorohydroxysulfide was dehydrohalogenated or a mercaptide was reacted with epichlorohydrin. Therefore, on the basis of the mercaptan used directly or to form intermediates, the mercaptide-epichlorohydrin method gave better overall yields.

Figure 4.

Refractive Index vs. Molecular Weight for Epoxypropyl Sulfides of the Type $RSCH_2\underline{CHCH_2}O$, R being Methyl through Hexyl

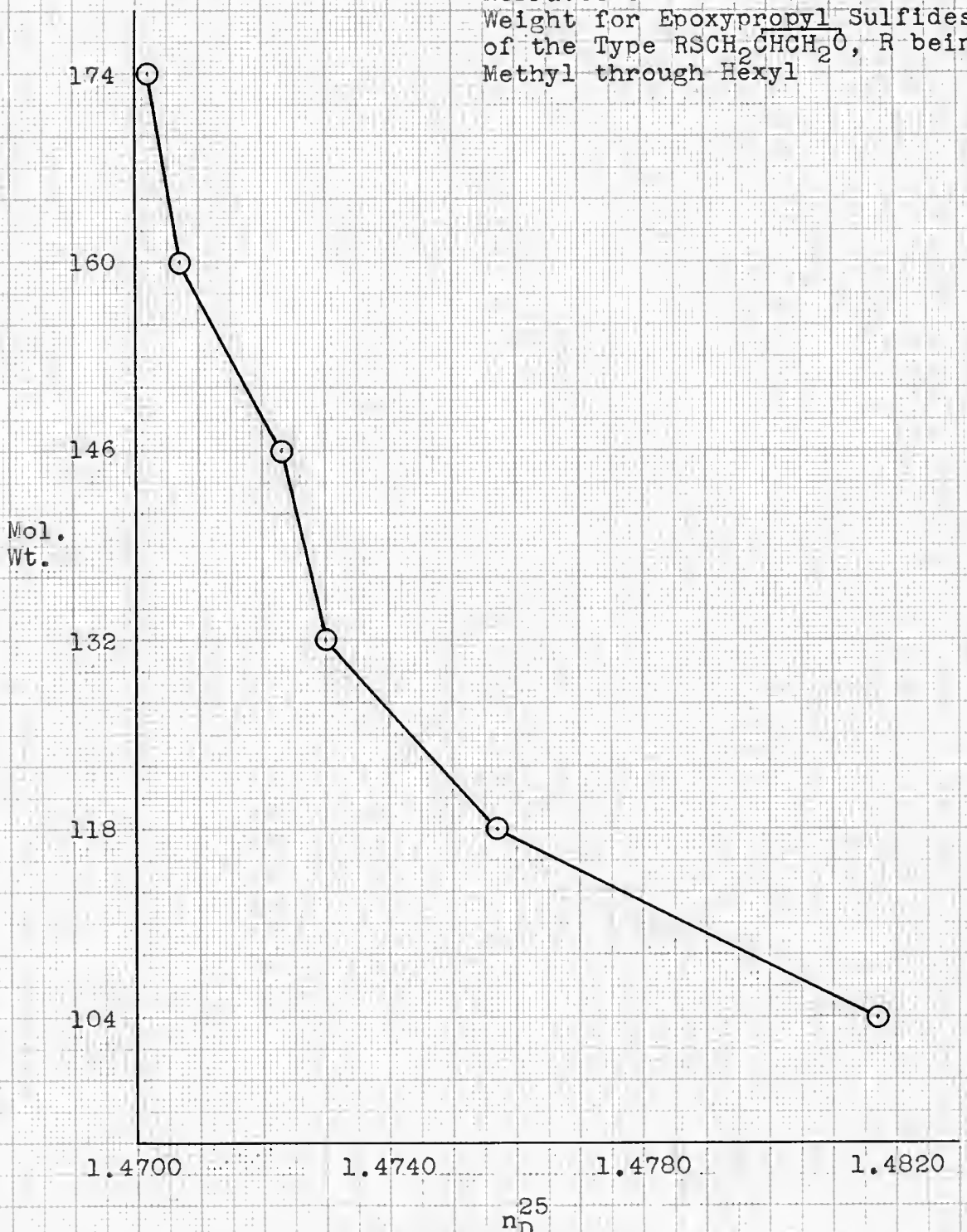


Figure 5.

Density vs. Molecular Weight for Epoxypropyl Sulfides of the Type $RSCH_2\overline{CHCH_2O}$, R being Methyl through Hexyl

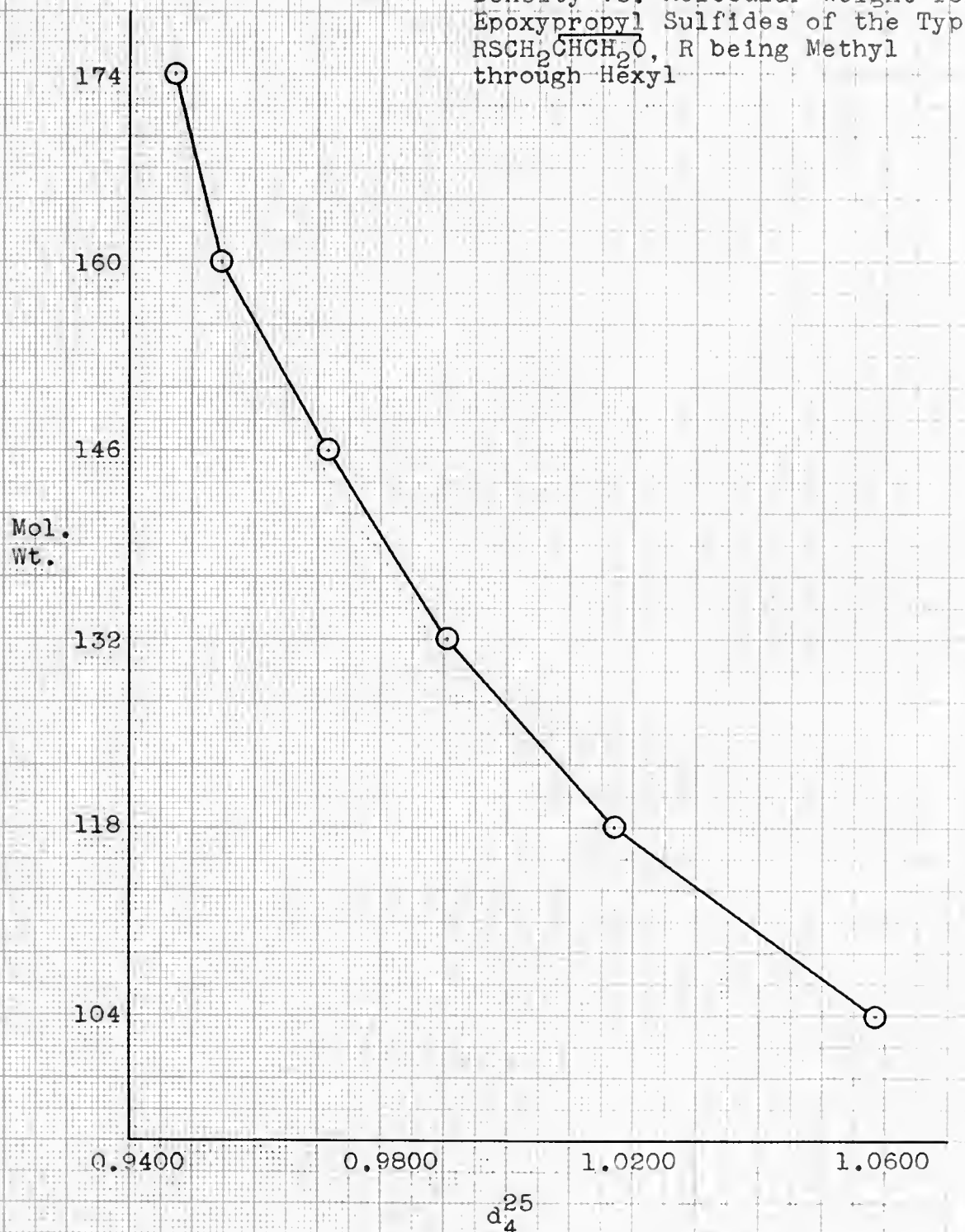
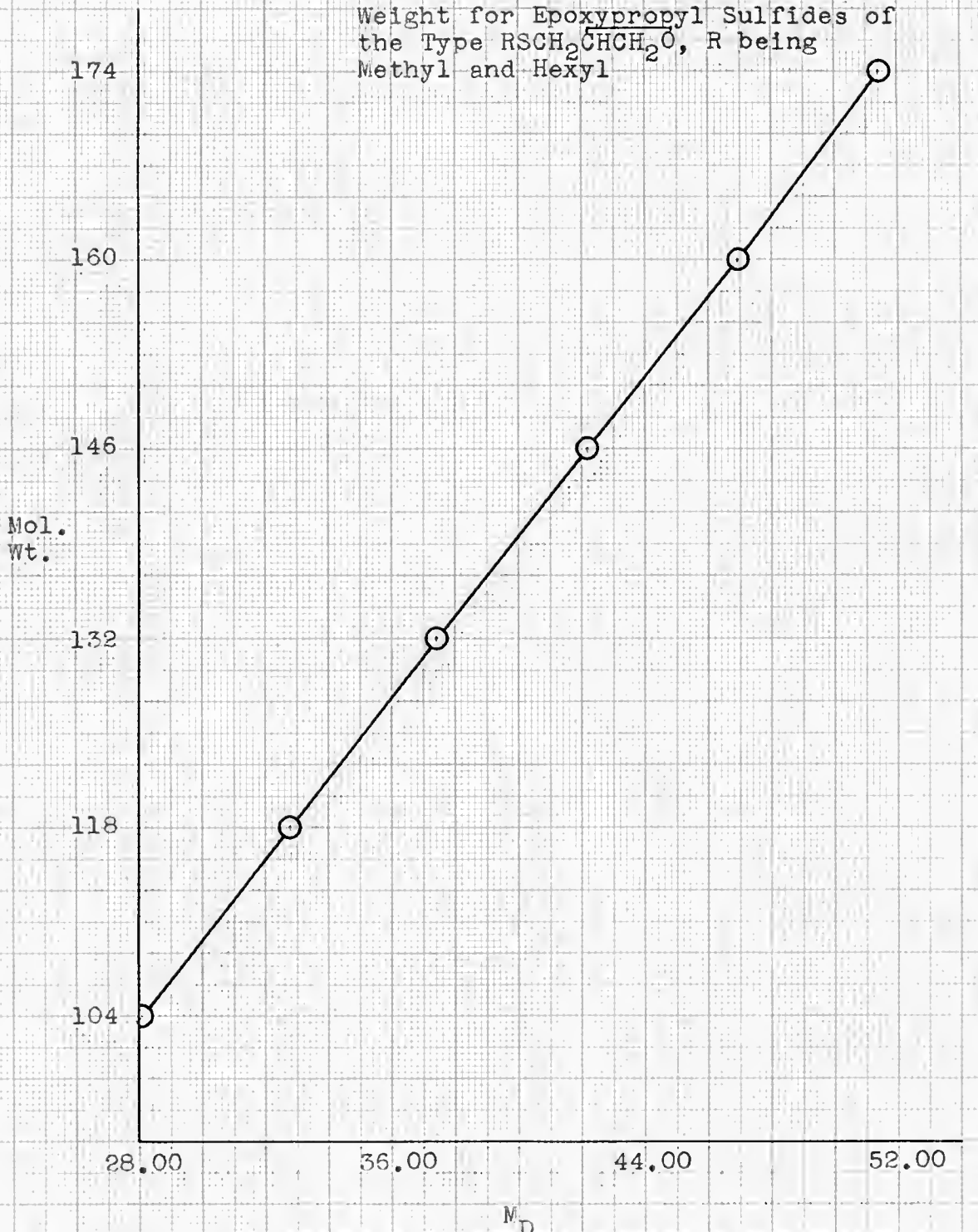


Figure 6.

Molecular Refraction vs. Molecular Weight for Epoxypropyl Sulfides of the Type $RSCH_2\underline{C}HCH_2O$, R being Methyl and Hexyl



4. Summary

Syntheses and physical properties were determined for the six epoxypropyl sulfides, methyl through hexyl. Synthesis of the ethyl and pentyl compounds, together with the physical properties of the ethyl compound, have been previously reported (3), (6).

C. Synthesis of hydroxydisulfides

1. Review of the literature

The dialkyl or diarylthiopropanols have been prepared in the following three ways: treatment of epichlorohydrin with an alkaline solution of a mercaptan, treatment of 1,3-dichloro-2-propanol with a mercaptide solution, and treatment of an alkylthiochloropropanol with a mercaptide solution.

1,3-bis(ethylthio)-2-propanol was synthesized from 1,3-dichloro-2-propanol and sodium ethyl mercaptide solution by Tschugaeff and Kobljanski (21). Fromm, Kappeller, and Taubmann (22) treated either epichlorohydrin or 1,3-dichloro-2-propanol with an alcoholic solution of sodium benzyl mercaptide to obtain 1,3-bis(benzylthio)-2-propanol. 1-benzylthio-3-ethylthio-2-propanol was prepared by Rothstein (7) from 1-ethylthio-3-chloro-2-propanol and sodium benzyl mercaptide solution. The Shell Development Company (6) reported treating epichlorohydrin with decyl or hydroxyethyl mercaptan, followed by treating the product with aqueous sodium hydroxide, to obtain 1,3-bis(decylthio)-2-propanol or 1,3-bis(2-hydroxyethyl)-

2-propanol, respectively.

2. Experimental

a. Synthesis of 1,3-bis(methylthio)-2-propanol

Reference is made to Section II,B,a,"Synthesis of 1-methylthio-2,3-epoxypropane", for procedure. 1,3-bis(methylthio)-2-propanol was collected at 159-161° at 50 mm.

B.P.	:	159-161° at 50 mm.
Yield	:	27.5 g., 0.35 mole, 17.4%
n_D^{25}	:	1.5359
d_4^{25}	:	1.1256
M_D	:	42.17 (found); 42.76 (calc.)
% C	:	39.63 (found); 39.47 (calc.)
% H	:	8.30 (found); 7.95 (calc.)

b. Synthesis of 1,3-bis(ethylthio)-2-propanol

0.5 mole (46 g.) of epichlorohydrin was placed in a 500 ml., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. A mercaptide-mercaptan mixture was prepared by dropwise addition of one mole (62 g.) of ethyl mercaptan to a cooled, stirred solution of 0.5 mole (33 g.) of 85% potassium hydroxide in 100 ml. of water. The mercaptide-mercaptan mixture was added dropwise to the cooled, stirred epichlorohydrin, the resulting mixture being stirred an additional two hours. The mix was then extracted with ethyl ether. The extract was dried over anhydrous calcium sulfate. The dried, filtered, ethereal solution was distilled

at 1 mm., 1,3-bis(ethylthio)-2-propanol being obtained at 93.8-94°.

B.P. : 93.8-94° at 1 mm.

Yield : 41 g., 0.23 mole, 46%

n_D^{25} : 1.5148

d_4^{25} : 1.0528

M_D : 51.63 (found); 51.99 (calc.)

% C : 46.33 (found); 46.62 (calc.)

% H : 9.24 (found); 8.95 (calc.)

c. Synthesis of 1,3-bis(propylthio)-2-propanol

0.43 mole (40 g.) of epichlorohydrin was placed in a 500 ml., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. A mercaptide-mercaptan mixture was prepared by dropwise addition of 0.86 mole (65 g.) of propyl mercaptan to a cooled, stirred solution of 28 g. of 85% potassium hydroxide in 100 ml. of water. The mixture was added dropwise to the cooled, stirred epichlorohydrin, the product being stirred an additional four hours. The mix was extracted with ethyl ether and the extract dried over anhydrous potassium carbonate. The dried, filtered solution was distilled, 1,3-bis(ethylthio)-2-propanol being collected at 104-105° under 0.7 mm.

B.P. : 104-105° at 0.7 mm.

Yield : 56 g., 0.28 mole, 64%

n_D^{25} : 1.5063

d_4^{25} : 1.0144

M_D : 61.06 (found); 61.23 (calc.)

% C : 51.56 (found); 51.90 (calc.)

% H : 9.77 (found); 9.68 (calc.)

d. Synthesis of 1,3-bis(butylthio)-2-propanol

0.09 mole (13 g.) of 1-butylthio-2,3-epoxypropane and 0.11 mole (10 g.) of butyl mercaptan were placed in a 200 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. The stirred mixture was heated to reflux and 0.2 gram of zinc chloride was added through the condenser. Heating was continued until a sudden clearing of the milky mixture, accompanied by a rapid rise in temperature, indicated completion of the reaction. The residue was distilled at 1 mm., 1,3-bis(butylthio)-2-propanol being obtained at 133°.

B.P. : 133° at 1 mm.

Yield : 11.5 g., 0.05 mole, 55%

n_D^{25} : 1.5007

d_4^{25} : 0.9867

M_D : 70.55 (found); 70.48 (calc.)

% C : 55.84 (found); 55.88 (calc.)

% H : 10.53 (found); 10.23 (calc.)

e. Synthesis of 1,3-bis(pentylthio)-2-propanol

0.15 mole (24.5 g.) of 1-pentylthio-2,3-epoxypropane and 0.15 mole (16 g.) of pentyl mercaptan were placed in a

200 ml., three-necked, round-bottomed flask, equipped with stirrer, thermometer, and reflux condenser. 0.5 gram of potassium hydroxide was added through the condenser while the mix was stirred rapidly. After five minutes, the temperature rose to the boiling point of the mercaptan, necessitating cooling. After apparent completion of the reaction, the mix was stirred an additional four hours. The product was dissolved in ether and the solution dried over potassium carbonate. The ether was removed and the residue distilled at 0.8 mm., 1,3-bis(pentylthio)-2-propanol being collected at 147.5-148.5°.

B.P. : 147.5-148.5° at 0.8 mm.

Yield : 27 g., 0.10 mole, 67%

n_D^{25} : 1.4960

d_4^{25} : 0.9692

M_D : 79.71 (found); 79.70 (calc.)

% C : 58.98 (found); 59.03 (calc.)

% H : 10.89 (found); 10.67 (calc.)

f. Synthesis of 1,3-bis(hexylthio)-2-propanol

0.10 mole (17.5 g.) of 1-hexylthio-2,3-epoxypropane and 0.10 mole (12 g.) of hexyl mercaptan were placed in a 200 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. While the solution was stirred rapidly, 0.5 gram of potassium hydroxide was added through the condenser. After five minutes, the temperature rose to reflux,

necessitating external cooling. After the reaction subsided, stirring was continued for four hours. The mix was dissolved in ether and the ethereal solution dried over potassium carbonate. Ether was removed and the residue distilled at 1.5 mm., 1,3-bis(hexylthio)-2-propanol being obtained at 183-184°.

B.P.	:	183-184° at 1.5 mm.
Yield	:	18.5 g., 0.06 mole, 63%
n_D^{25}	:	1.4927
d_4^{25}	:	0.9547
M_D	:	89.00 (found); 88.94 (calc.)
% C	:	61.21 (found); 61.58 (calc.)
% H	:	10.54 (found); 11.03 (calc.)

3. Discussion of experimental results

While it would appear from the yields given that the reaction of mercaptans with epoxysulfides is more advantageous than the reaction of epichlorohydrin with an excess of mercaptide solution for preparation of hydroxydisulfides, consideration of the time required to prepare the intermediate epoxysulfides and inclusion of the fact that these epoxysulfides are obtained in 50% yields leads to the conclusion that the advantage lies with the latter method.

Figures 7, 8 and 9 indicate the variation in physical properties of the hydroxydisulfides from dimethyl through dihexyl.

Figure 7.

Refractive Index vs. Molecular Weight for Hydroxydisulfides of the Type $RSCH_2CHOHCH_2SR$, R being Methyl through Hexyl

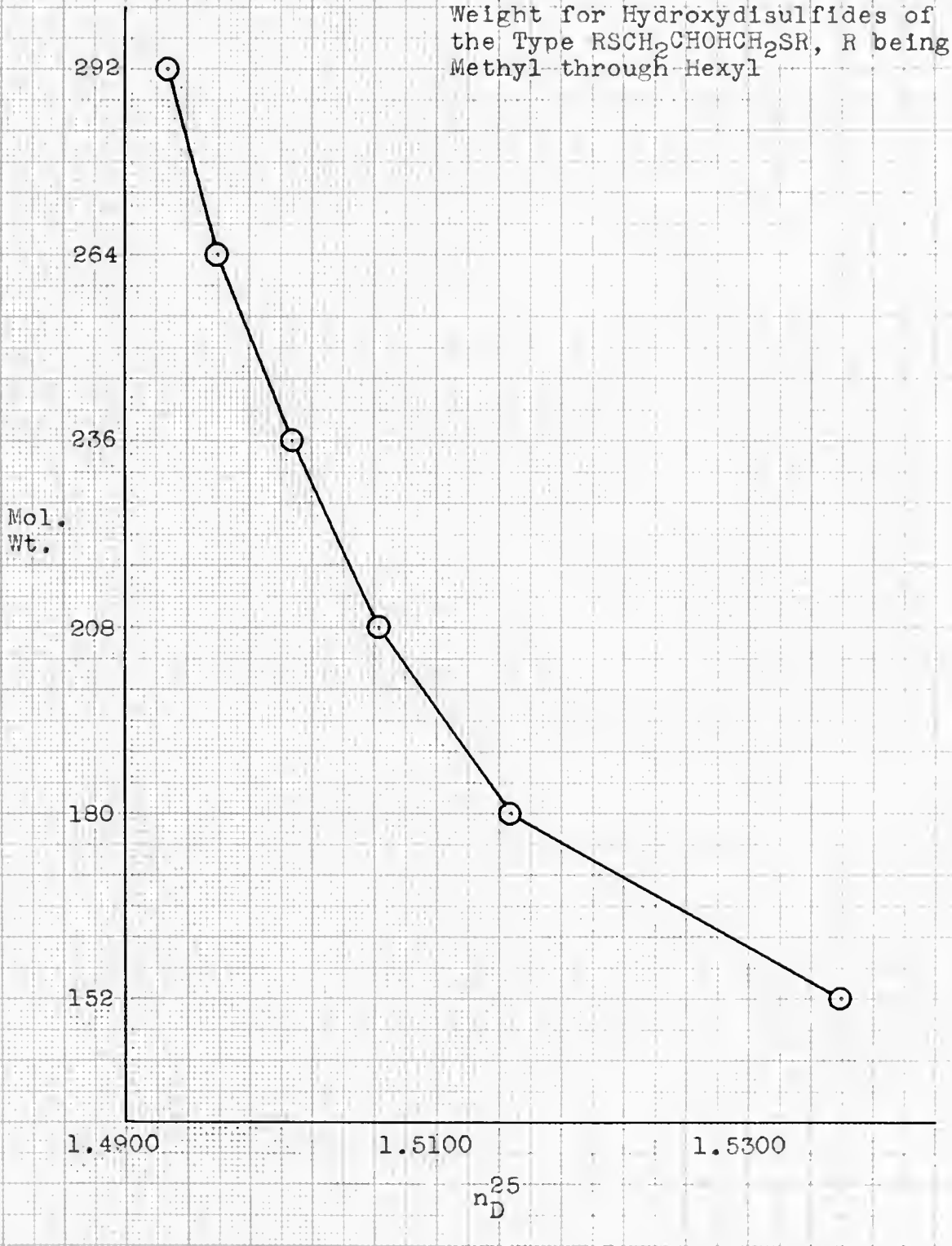


Figure 8.

Density vs. Molecular Weight for Hydroxydisulfides of the Type $RSCH_2CHOHCH_2SR$, R being Methyl through Hexyl

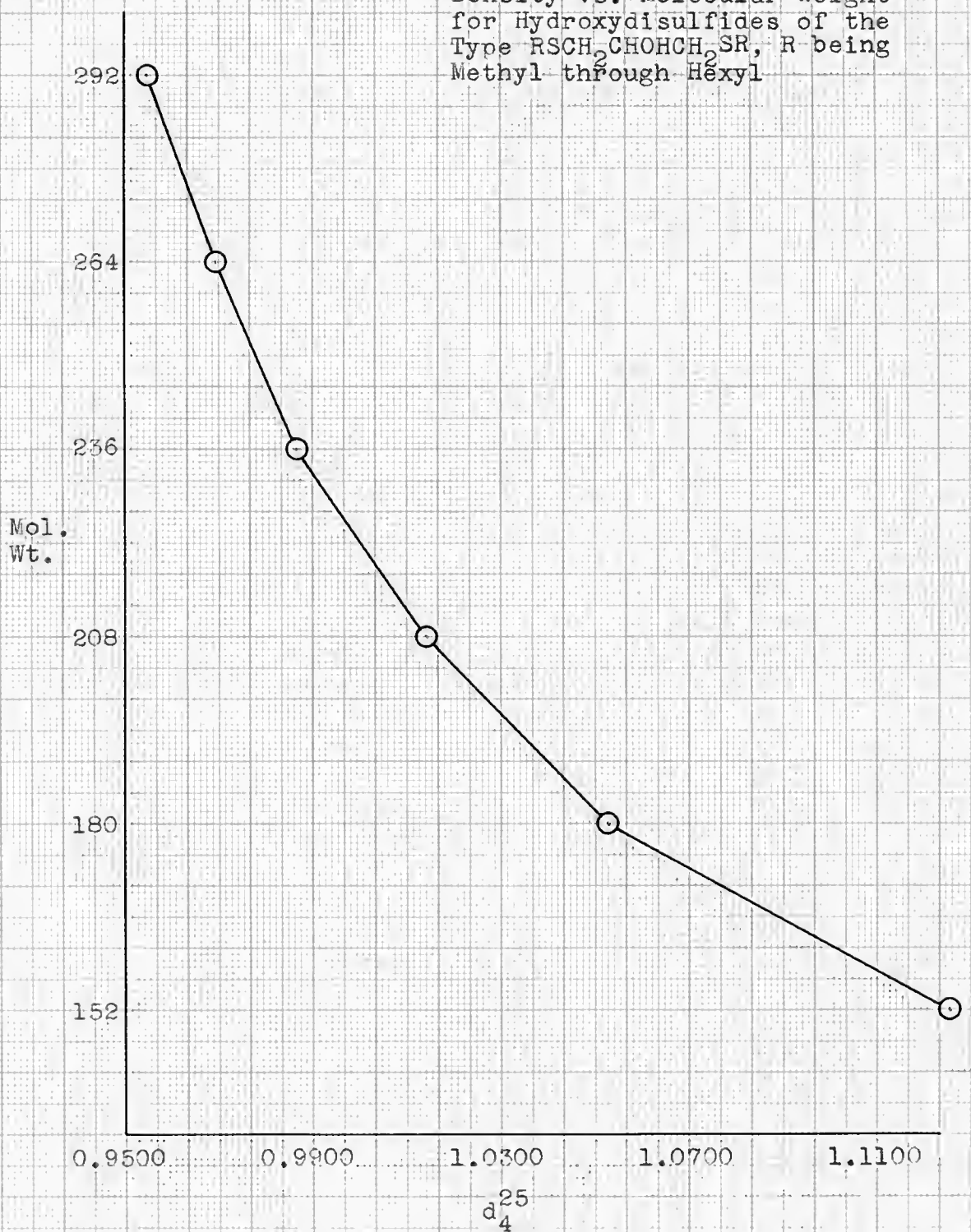
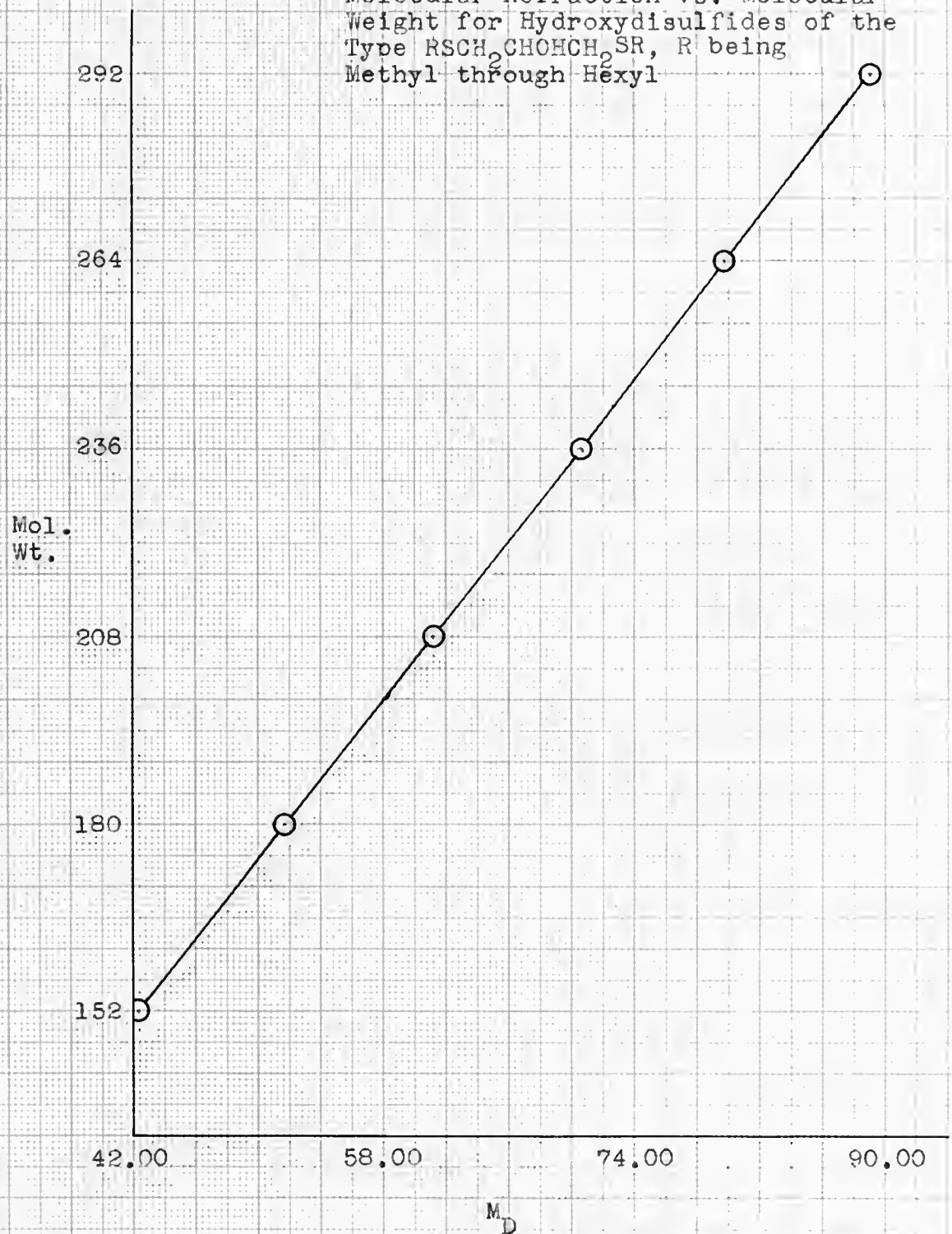


Figure 9.

Molecular Refraction vs. Molecular Weight for Hydroxydisulfides of the Type $RSCH_2CHOHCH_2SR$, R being Methyl through Hexyl



4. Summary

Syntheses are given for six 1,3 bis(alkylthio) propanols. Only 1,3-bis(ethylthio)-2-propanol has been reported previously.

D. Synthesis of chlorohydroxypropyl sulfones

1. Review of literature

Sulfones have been prepared by oxidation of sulfides and sulfoxides with potassium permanganate, chromic anhydride, sodium dichromate, nitric acid, sodium hypochlorite, chlorine, hydrogen peroxide, and various organic peroxides and peracids in a variety of solvents. In addition, the action of metal sulfinates on organic halides and the action of metal alkyls on sulfonyl halides have been used as means for the preparation of sulfones. Suter (23) lists over 500 references dealing with these compounds.

Chlorohydroxypropyl sulfones have been prepared by oxidation of the corresponding chlorohydroxypropyl sulfides. Nenitzescu and Scarlatescu (3) oxidized 1-phenylthio-3-chloro-2-propanol to 1-phenylsulfonyl-3-chloro-2-propanol with potassium permanganate. Rothstein (7) obtained 1-ethylsulfonyl-3-chloro-2-propanol and 1-benzylsulfonyl-3-chloro-2-propanol by oxidation of the sulfides in acetic acid solution with 30% hydrogen peroxide.

2. Experimental

a. Synthesis of 1-methylsulfonyl-3-chloro-2-propanol

Fourteen grams of 1-methyl thio-3-chloro-2-propanol and

50 ml. of glacial acetic acid were placed in a 250 ml. beaker. To this solution 30 ml. of 30% hydrogen peroxide was added dropwise with stirring, at such a rate that ebullition did not become too violent. Acetic acid, water and excess hydrogen peroxide were removed under aspirator vacuum while heating on the steam bath. The residue slowly crystallized over two days and was recrystallized from ethyl ether.

M.P. : 58.7-59.0°

Yield : 13 g., 76.5%

% C : 27.42 (found); 27.83 (calc.)

% H : 5.16 (found); 5.26 (calc.)

b. Synthesis of 1-ethylsulfonyl-3-chloro-2-propanol

Ten grams of 1-ethylthio-3-chloro-2-propanol and 50 ml. of glacial acetic acid were placed in a 250 ml. beaker. 30 ml. of 30% hydrogen peroxide was added dropwise with stirring, at such a rate as to maintain gentle ebullition. Acetic acid, water, and excess hydrogen peroxide were removed by evaporation on the steam bath. The highly viscous residue crystallized very slowly in the ice-box. The solidified material was recrystallized from ethyl ether. (The hygroscopic character of this and the preceding compound made recrystallization very difficult).

M.P. : 47.5-48.5°

Yield : 10 g., 83%

% C : 31.78 (found); 32.17 (calc.)

% H : 6.02 (found); 5.94 (calc.)

c. Synthesis of 1-propylsulfonyl-3-chloro-2-propanol

In a 250 ml. beaker were placed ten grams of 1-propylthio-3-chloro-2-propanol and 50 ml. of glacial acetic acid. 30 ml. of 30% hydrogen peroxide was added dropwise with stirring, at such a rate as to maintain gentle ebullition. The resulting mixture was evaporated to a thick syrup on the steam bath and set in the icebox to crystallize. The solidified material was recrystallized from ethyl ether.

M.P. : 48-49°

Yield : 8 g., 67%

% C : 35.92 (found); 35.91 (calc.)

% H : 6.55 (found); 6.53 (calc.)

d. Synthesis of 1-butylsulfonyl-3-chloro-2-propanol

In a 100 ml. beaker were placed ten grams of 1-butylthio-3-chloro-2-propanol and 30 ml. of glacial acetic acid. 25 ml. of 30% hydrogen peroxide was added dropwise with stirring, at such a rate that gentle ebullition was maintained. The resulting solution was evaporated on a steam bath to a thick syrup which crystallized on standing. The solid product was recrystallized from acetone and from 95% ethanol.

M.P. : 57-57.3°

Yield : 10 g., 85%

% C : 38.98 (found); 39.16 (calc.)

% H : 7.28 (found); 7.04 (calc.)

e. Synthesis of 1-pentylsulfonyl-3-chloro-2-propanol

In a 100 ml. beaker were placed five grams of 1-pentylthio-3-chloro-2-propanol and 15 ml. of glacial acetic acid. 10 ml. of 30% hydrogen peroxide was added dropwise with stirring. After the vigorous reaction was completed, the resulting mixture was evaporated to a thick syrup on the steam bath. The syrup crystallized on standing, the solid being recrystallized from 95% ethanol and from acetone.

M.P. : 58.4-58.7°

Yield : 5.3 g., 90%

% C : 42.02 (found); 42.00 (calc.)

% H : 7.69 (found); 7.49 (calc.)

f. Synthesis of 1-hexylsulfonyl-3-chloro-2-propanol

In a 250 ml. beaker were placed ten grams of 1- hexylthio-3-chloro-2-propanol and 50 ml. of glacial acetic acid. 30 ml. of 30% hydrogen peroxide was added dropwise with stirring. After the vigorous reaction had ceased, the remaining solution was evaporated to a syrup on the steam bath. The syrup solidified on standing, the solid being recrystallized from ethyl ether, acetone and 95% ethanol.

M.P. : 59.5-59.8°

Yield : 4.5 g., 40%

% C : 44.19 (found); 44.52 (calc.)

% H : 8.22 (found); 7.89 (calc.)

3. Discussion of experimental results

Hydrogen peroxide was chosen as the oxidizing agent in these syntheses because its use does not ordinarily lead to undesirable side reactions and the water, acetic acid, and excess peroxide are easily removed, leaving the desired product in a relatively pure state as a residue.

It is probable that distillation would be a better means of purification of the first three members of this series than is crystallization, due to their low melting points, their hygroscopic character and their marked tendency to supercool. Distillation of the ethyl compound at 0.5 mm. was attempted, with decomposition resulting. Rothstein (7) was able to distil the latter substance at 141° at 0.1 mm.

After two recrystallizations, the last three compounds of the series all melted in the range, 57-58°. As many as ten recrystallizations were necessary to obtain the points given.

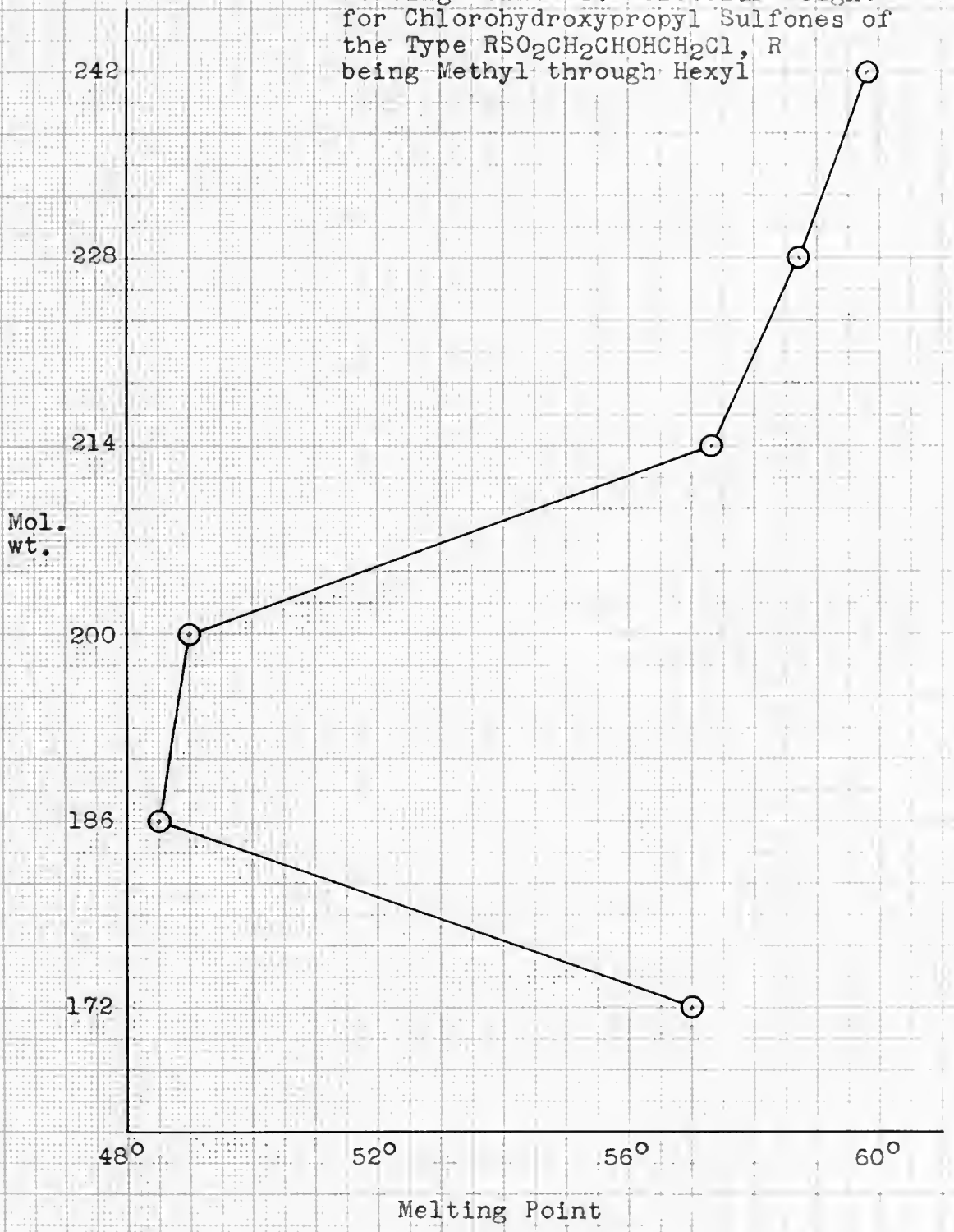
Figure 10 shows the change in melting point of these substances as their molecular weight increases. It is remarkable that there is such slight variation in this property.

4. Summary

Syntheses have been presented for six chlorohydroxypropyl sulfones, one of which, ethylsulfonylchloropropanol, has been previously reported (7), the others being new to the literature.

Figure 10.

Melting Point vs. Molecular Weight for Chlorohydroxypropyl Sulfones of the Type $RSO_2CH_2CHOHCH_2Cl$, R being Methyl through Hexyl



E. Synthesis of epoxypropyl sulfones

1. Review of the literature

Reference is made to Section II,B,1 and Section II,D,1 of this report for reviews of the preparation of epoxides and sulfones, respectively.

Epoxypropyl sulfones appear to be a new class of compounds, there being no reference to them in the literature.

2. Experimental

a. Synthesis of 1-methylsulfonyl-2,3-epoxypropane

In a 100 ml. beaker was placed a solution of five grams of 1-methylsulfonyl-3-chloro-2-propanol in 10 ml. of water. To this cooled, stirred solution was added dropwise an ice-cold solution of ten grams of 85% potassium hydroxide in 10 ml. of water. Stirring was continued for two hours. The resulting mixture was diluted with 20 ml. of water and the solid material collected by filtration. Purification was effected by successive washing with water, ethanol, and acetone, since the product appeared insoluble in any solvent other than a strong mineral acid.

M.P. : 260-261°d.

Yield : 3 g., 75%

% C : 35.54 (found); 35.28 (calc.)

% H : 6.32 (found); 5.92 (calc.)

b. Synthesis of 1-ethylsulfonyl-2,3-epoxypropane

In a 25 ml. beaker was placed a solution of 0.6 gram of

1-ethylsulfonyl-3-chloro-2-propanol in 5 ml. of water. To this cooled, stirred solution was slowly added one gram of powdered 98% sodium hydroxide. After fifteen minutes, the solid formed was taken up in acetone and recrystallized from the same solvent.

M.P. : 225-226°

Yield : 0.15 g., 31%

% C : 39.81 (found); 39.98 (calc.)

% H : 6.96 (found); 6.71 (calc.)

c. Synthesis of 1-propylsulfonyl-2,3-epoxypropane

In a 25 ml. beaker was placed a solution of one gram of 1-propylsulfonyl-3-chloro-2-propanol in 5 ml. of water. To this cooled, stirred solution was slowly added two grams of powdered 98% sodium hydroxide. After fifteen minutes, the solid formed was taken up in acetone and recrystallized from the same solvent.

M.P. : 193-194°

Yield : 0.5 g., 61%

% C : 44.00 (found); 43.88 (calc.)

% H : 7.42 (found); 7.37 (calc.)

d. Synthesis of 1-butylsulfonyl-2,3-epoxypropane

In a 25 ml. beaker was placed a suspension of one gram of 1-butylsulfonyl-3-chloro-2-propanol in 5 ml. of water. To this cooled, stirred suspension was added, slowly, two grams of powdered 98% sodium hydroxide. After 15 minutes

the solid formed was taken up in acetone and recrystallized from the same solvent.

M. P. : 169-170°

Yield : 0.75 g., 90%

% C : 47.45 (found); 47.17 (calc.)

% H : 8.35 (found); 7.93 (calc.)

Mol.Wt. : 179 (found); 176 (calc.)

e. Synthesis of 1-pentylsulfonyl-2,3-epoxypropane

In a 100 ml. beaker was placed a suspension of 1.28 grams of 1-pentylsulfonyl-3-chloro-2-propanol in 25 ml. of water. To this was added a solution of two grams of sodium hydroxide in 25 ml. of water. The mixture was warmed to 70° with stirring, cooled, and the impure 1-pentylsulfonyl-2,3-epoxypropane filtered off. The material was recrystallized from acetone.

M.P. : 160-161°

Yield : 0.70 g., 65%

% C : 49.92 (found); 49.97 (calc.)

% H : 8.71 (found); 8.39 (calc.)

f. Synthesis of 1-hexylsulfonyl-2,3-epoxypropane

In a 100 ml. beaker was placed a solution of two grams of 1-hexylsulfonyl-3-chloro-2-propanol in 25 ml. of 50% aqueous ethanol. To this cooled, stirred solution was added dropwise a solution of five grams of potassium hydroxide in 25 ml. of 50% ethanol. The mixture was stirred for one hour,

diluted with an equal volume of water and filtered to remove the crude 1-hexylsulfonyl-2,3-epoxypropane. The material was recrystallized from acetone.

M.P. : 178-179°

Yield : 1.5 g., 86%

% C : 52.35 (found); 52.39 (calc.)

% H : 9.04 (found); 8.79 (calc.)

3. Discussion of experimental results

In view of the unexpectedly high melting points of this series of compounds, it was thought that there was a possibility of the compounds existing as dimers or even higher polymers of the simple epoxypropyl sulfones. To further investigate this possibility, the molecular weight of the supposed butylsulfonyl-epoxypropane was determined by the Rast camphor method (24). Since the determined value checked the calculated value for the monomer, it may be assumed that these are truly epoxypropyl sulfones, rather than bis(/alkyl sulfonyl/methyl)dioxanes, for example.

Generally, optimum yields were attained for this series when the reaction temperature was below 10°. The anomalous preparation of the pentyl derivative, using elevated temperatures, has not been explained.

The compounds appear to be decomposed slowly upon long heating with aqueous acid or base, probably through rupture of, and addition of water to, the epoxide ring.

Figure 11 shows the variation in the melting points of the series as the molecular weight increases.

4. Summary

Syntheses for six members of a new series of compounds, the epoxypropyl sulfones, have been proposed.

F. Synthesis of hydroxydisulfones

1. Review of the literature

The formation of sulfones was summarized in Section II, D, 1 of this investigation.

Hydroxydisulfones have been prepared by oxidation of the corresponding disulfides. Fromm, Kappeller, and Taubmann (22) oxidized 1,3-bis(benzylthio)-2-propanol with potassium permanganate to obtain 1,3-bis(benzylsulfonyl)-2-propanol. Rothstein (7) synthesized 1,3-bis(ethylsulfonyl)-2-propanol and 1-benzylsulfonyl-3-ethylsulfonyl-2-propanol from the corresponding sulfides by oxidation in acetic acid solution with 30% hydrogen peroxide.

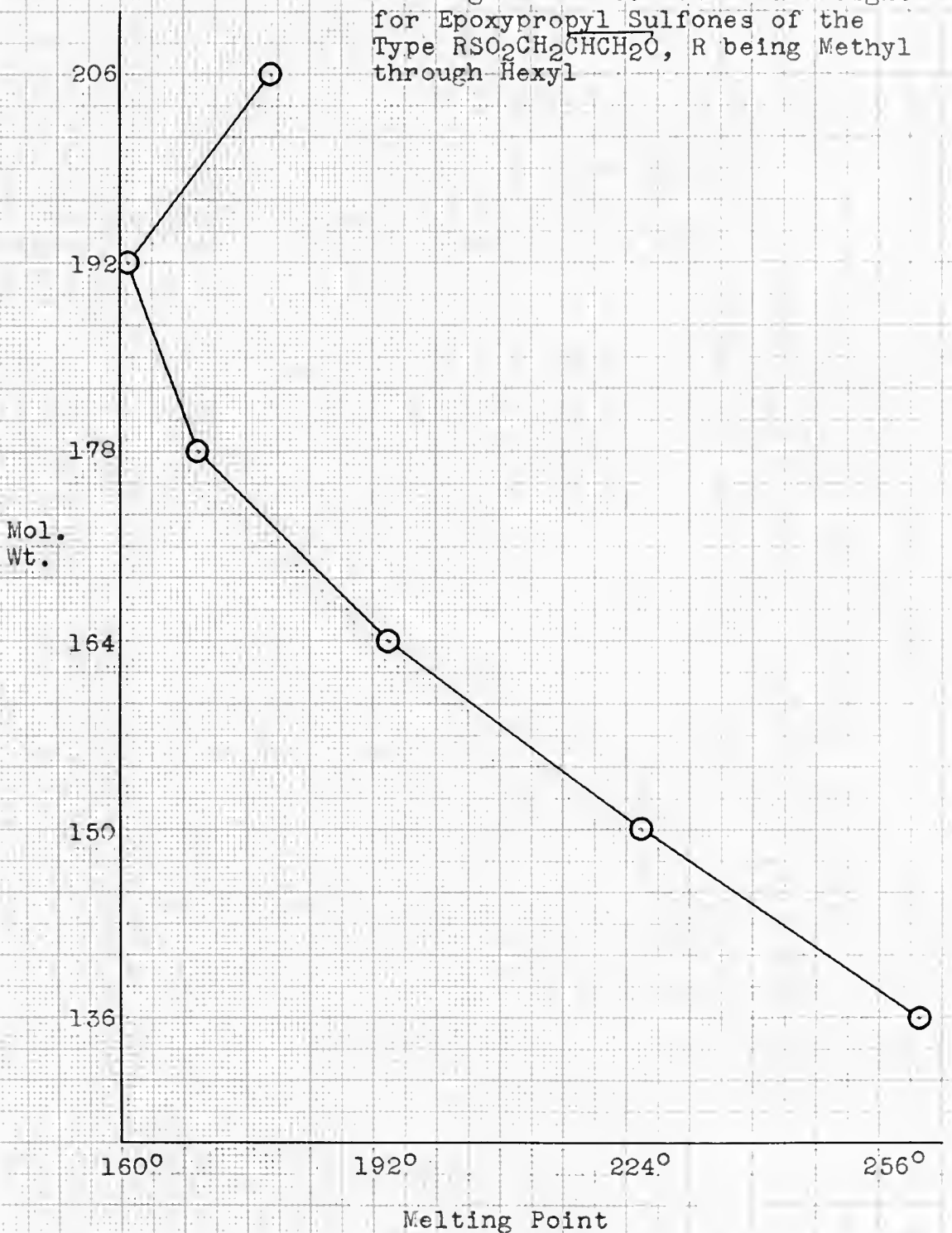
2. Experimental

a. Synthesis of 1,3-bis(methylsulfonyl)-2-propanol

In a 100 ml. beaker was placed three grams of 1,3-bis (methylthio)-2-propanol and 15 ml. of glacial acetic acid. To this solution was added dropwise, with stirring, 12 ml. of 30% hydrogen peroxide. After the reaction subsided, most of the water and acetic acid was evaporated on a steam bath, the residue cooled, and the crude bis(methylsulfonyl) propanol

Figure 11.

Melting Point vs. Molecular Weight for Epoxypropyl Sulfones of the Type $RSO_2CH_2\overline{CHCH_2O}$, R being Methyl through Hexyl



filtered off and recrystallized from 95% ethanol.

M.P. : 136-137°

Yield : 3.9 g., 93%

% C : 27.28 (found); 27.77 (calc.)

% H : 5.92 (found); 5.59 (calc.)

b. Synthesis of 1,3-bis(ethylsulfonyl)-2-propanol

In a 100 ml. beaker were placed two grams of 1,3-bis (ethylthio)-2-propanol and 15 ml. of glacial acetic acid. 12 ml. of 30% hydrogen peroxide was added dropwise, with stirring. After the reaction subsided, the solution was evaporated on a steam bath to a small volume. Crude 1,3-bis (ethylsulfonyl)-2-propanol separated on cooling, was filtered off, and recrystallized from 95% ethanol.

M.P. : 113-114°

Yield : 1.5 g., 70%

% C : 34.45 (found); 34.41 (calc.)

% H : 6.70 (found); 6.60 (calc.)

c. Synthesis of 1,3-bis(propylsulfonyl)-2-propanol

In a 100 ml. beaker were placed five grams of 1,3-bis (propylthio)-2-propanol and 20 ml. of glacial acetic acid. 15 ml. of 30% hydrogen peroxide was added slowly with stirring. The mixture was allowed to stand overnight, then evaporated to incipient crystallization on a steam bath. 20 ml. of water was added and the crude 1,3-bis(propylsulfonyl)-2-propanol filtered off and recrystallized from 95% ethanol.

M.P. : 155-156°

Yield : 5.5 g., 84%

% C : 39.99 (found); 39.68 (calc.)

% H : 7.56 (found); 7.40 (calc.)

d. Synthesis of 1,3-bis(butylsulfonyl)-2-propanol

In a 100 ml. beaker were placed five grams of 1,3-bis (butylthio)-2-propanol and 20 ml. of glacial acetic acid. 12 ml. of 30% hydrogen peroxide was added slowly, with stirring. After the vigorous reaction had subsided, the solution was evaporated on a steam bath to incipient crystallization, 20 ml. of water was added and the crude product filtered off. Recrystallization was from 95% ethanol.

M.P. : 135-136°

Yield : 4.5 g., 71%

% C : 43.92 (found); 43.97 (calc.)

% H : 8.19 (found); 8.05 (calc.)

e. Synthesis of 1,3-bis(pentylsulfonyl)-2-propanol

In a 250 ml. beaker were placed thirteen grams of 1,3-bis(pentylthio)-2-propanol and 50 ml. of glacial acetic acid. 35 ml. of 30% hydrogen peroxide was added slowly, with stirring. The solution was allowed to stand overnight. The crude product was filtered off and recrystallized from 95% ethanol.

M.P. : 143-144°

Yield : 10 g., 60%

% C : 47.69 (found); 47.53 (calc.)

% H : 9.03 (found); 8.59 (calc.)

f. Synthesis of 1,3-bis(hexylsulfonyl)-2-propanol

In a 250 ml. beaker were placed eighteen grams of crude 1,3-bis(hexylthio)-2-propanol and 50 ml. of glacial acetic acid. 35 ml. of 30% hydrogen peroxide was added slowly, with stirring. The solution was allowed to stand overnight. The crude product was filtered off and recrystallized from 95% ethanol.

M.P. : 149-150°

Yield : 11.5 g., 53%

% C : 50.59 (found); 50.52 (calc.)

% H : 9.29 (found); 9.05 (calc.)

3. Discussion of experimental results

Though Fromm, Kappeller, and Taubmann (22) found that bis(benzylsulfonyl)propanol crystallized from aqueous alcohol with a molecule of water, this phenomenon was not observed with the compounds of the series herein reported.

It is noteworthy that the melting point of the propyl derivative is anomalous, in that it is unexpectedly high. However, the same compound was obtained from the disulfide synthesized by different methods.

Generally, the compounds were colorless (white), waxy platelets, readily prepared in good yields by the methods described.

Figure 12 indicates the variation in the melting points of the compounds as the molecular weight increases.

4. Summary

Syntheses of six bis(alkylsulfonyl)propanols, methyl through hexyl, are described. The ethyl derivative has been previously reported (7).

G. Synthesis of alkylthioalkoxypropanols

1. Review of the literature

Mixed sulfur-oxygen ethers have been the subject of very little study. Clarke (25) obtained 1-methylthio-2-methoxyethane from the action of sodium ethyl mercaptide on 1-iodo-2-methoxyethane in methanol. One investigator (26), used a modified Williamson synthesis to obtain mixed ethers from the interaction of zinc, alcohols, and mustard gas.

Formation of hydroxy ethers by treatment of epoxides with alcohols in the presence of various catalysts has been reported by many investigators (1), (8), (9), (27), (28), (29), (30), (31).

No mixed ethers of the type herein reported (derived from thioglycerol) appear in the literature.

2. Experimental

a. Synthesis of 1-ethylthio-3-methoxy-2-propanol

A solution of 1.6 grams of metallic sodium in 2.5 moles (80 g.) of methanol was placed in a 500 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and

reflux condenser. To this stirred solution was added, dropwise, through the condenser, 0.25 mole (30 g.) of 1-ethylthio-2,3-epoxypropane. No temperature rise was noted. The solution was then refluxed for three hours. Most of the methanol was removed at atmospheric pressure, the sodium methylate present neutralized with 6N sulfuric acid, and the distillation continued at 9 mm. 1-ethylthio-3-methoxy-2-propanol was obtained at 92.5-92.8°.

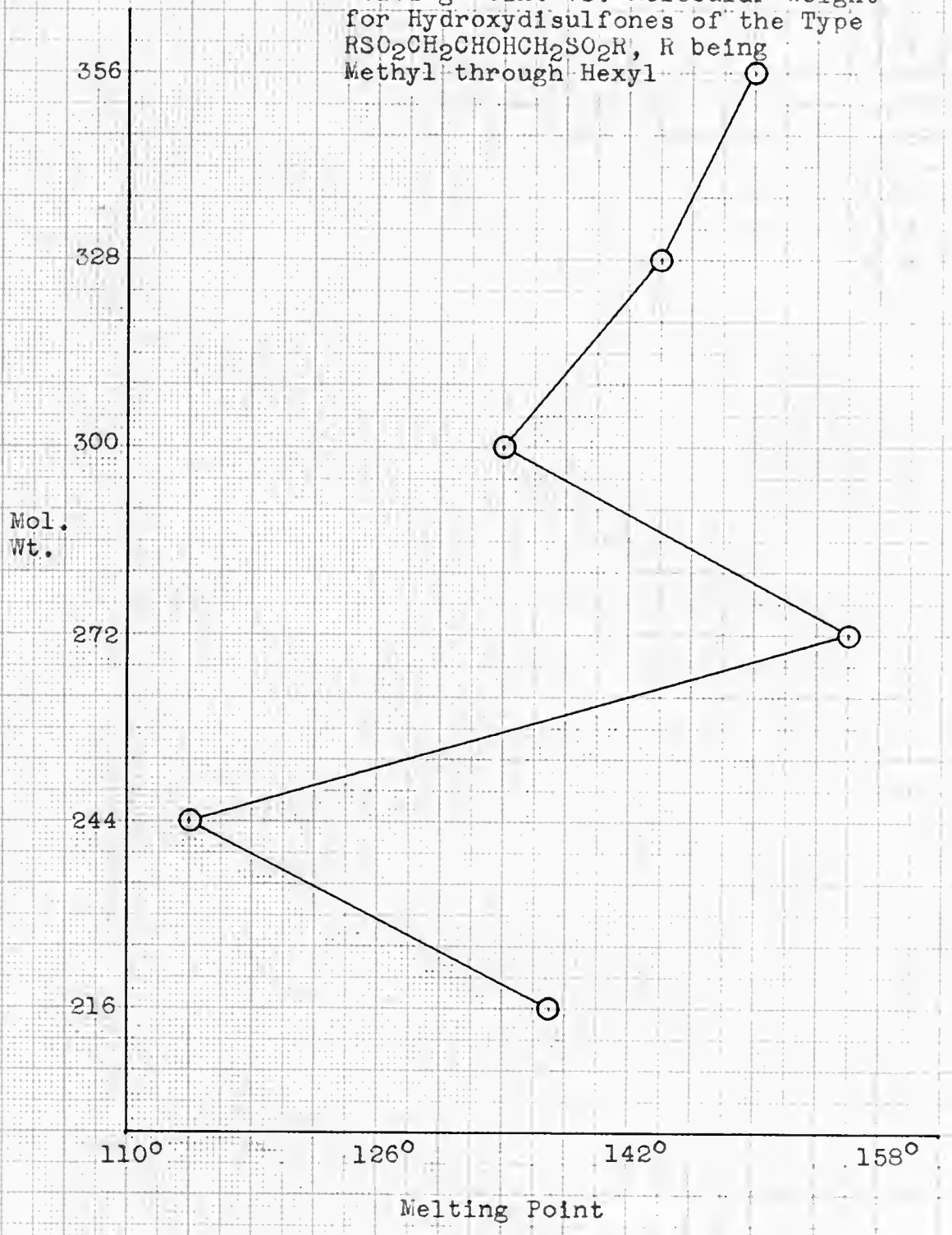
B.P.	:	92.5-92.8° at 9 mm.
Yield	:	23.5 g., 0.15 mole, 62%
n_D^{25}	:	1.4734
d_4^{25}	:	1.0322
M_D	:	40.86 (found); 41.05 (calc.)
% C	:	48.24 (found); 47.97 (calc.)
% H	:	9.52 (found); 9.39 (calc.)

b. Synthesis of 1-ethylthio-3-ethoxy-2-propanol

A solution of one mole (66 g.) of 85% potassium hydroxide in five moles (240 g.) of 95% ethanol was placed in a 500 ml., three-necked, round-bottomed flask, equipped with stirrer, reflux condenser, and dropping funnel. To this cooled, stirred solution was added dropwise one mole (62 g.) of ethyl mercaptan. In a similarly equipped one liter flask was placed one mole (92 g.) of epichlorohydrin. The ethanol solution of potassium ethyl mercaptide was added dropwise to the cooled stirred epichlorohydrin. After all of the solution had been added,

Figure 12.

Melting Point vs. Molecular Weight for Hydroxydisulfones of the Type $RSO_2CH_2CHOHCH_2SO_2R$, R being Methyl through Hexyl



the cooling bath was removed and the temperature rose to 60°. Stirring was continued for four hours. The product was filtered and dried overnight with anhydrous potassium carbonate. Excess ethanol was removed from the dried solution at atmospheric pressure, the residue being distilled at 40 mm. 1-ethylthio-3-ethoxy-2-propanol was collected at 136-137°.

B.P.	:	136-137° at 40 mm.
Yield	:	56.5 g., 0.34 mole, 34%
n_D^{25}	:	1.4679
d_4^{25}	:	1.0037
M_D	:	45.49 (found); 45.66 (calc.)
% C	:	50.78 (found); 51.16 (calc.)
% H	:	10.06 (found); 9.81 (calc.)

c. Synthesis of 1-ethylthio-3-propoxy-2-propanol

A solution of 1.6 grams of metallic sodium in 2.0 moles (120 g.) of propanol-1 was placed in a 500 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. 0.25 mole (30 g.) of 1-ethylthio-2,3-epoxypropane was added dropwise to the stirred solution through the condenser. No temperature change was observed during one hour. The stirred mix was then heated to reflux for five hours. The cooled product was neutralized with 6N sulfuric acid, five grams of potassium carbonate added, and the mixture allowed to stand overnight. The solid was fil-

tered off and the filtrate distilled, 1-ethylthio-3-propoxy-2-propanol being obtained at 78-78.5° at 2 mm.

B.P.	:	78-78.5° at 2 mm.
Yield	:	29 g., 0.16 mole, 65%
n_D^{25}	:	1.4661
d_4^{25}	:	0.9837
M_D	:	50.20 (found); 50.28 (calc.)
% C	:	53.97 (found); 53.89 (calc.)
% H	:	10.62 (found); 10.18 (calc.)

d. Synthesis of 1-ethylthio-3-butoxy-2-propanol

1.34 moles (100 g.) of butanol-1 and 1.6 grams of metallic sodium was placed in a 500 ml., three-necked, round-bottomed flask, equipped with a stirrer, thermometer and reflux condenser. To this stirred solution was added, dropwise, 0.25 mole (30 g.) of 1-ethylthio-2,3-epoxypropane. After being stirred for two hours without a rise in temperature, the mix was heated to 75-80° during six hours. The cooled product was neutralized with 1:1 hydrochloric acid, 100 ml. of water added, and the mixture extracted twice with ethyl ether. The combined extracts were dried over anhydrous potassium carbonate. Ethyl ether and excess butanol were distilled off at atmospheric pressure. The residue was distilled at 2 mm., 1-ethylthio-3-butoxy-2-propanol being collected at 85.5-86.5°.

B.P. : 85.5-86.5° at 2 mm.

Yield : 33.5 g., 0.17 mole, 69.5%

n_D^{25} : 1.4652

d_4^{25} : 0.9695

M_D : 54.91 (found); 54.90 (calc.)

% C : 55.91 (found); 56.20 (calc.)

% H : 10.47 (found); 10.48 (calc.)

e. Synthesis of 1-propylthio-3-methoxy-2-propanol

A solution of 1.6 grams of metallic sodium in 2.5 moles (80 g.) of methanol was placed in a 500 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. To this stirred solution was added, dropwise, through the condenser, 0.25 mole (33 g.) of 1-propylthio-2,3-epoxypropane. The mixture was refluxed for three hours, cooled, and neutralized with 6N sulfuric acid. The neutralized mixture was dried over anhydrous potassium carbonate and distilled. 1-propylthio-3-methoxy-2-propanol was collected at 65-66° at 2 mm.

B.P. : 65-66° at 2 mm.

Yield : 20 g., 0.12 mole, 49%

n_D^{25} : 1.4719

d_4^{25} : 1.0095

M_D : 45.55 (found); 45.66 (calc.)

% C : 50.98 (found); 51.18 (calc.)

% H : 10.14 (found); 9.82 (calc.)

f. Synthesis of 1-propylthio-3-ethoxy-2-propanol

1.3 grams of metallic sodium and 2.2 moles (100 g.) of ethanol were placed in a 500 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. 0.2 mole (26.5 g.) of 1-propylthio-2,3-epoxypropane was added through the condenser to the stirred solution. There was no temperature change during one hour's stirring. The stirred mix was then heated to reflux for three hours, cooled, neutralized with 6N sulfuric acid, and five grams of potassium carbonate added. The mixture was left in the icebox overnight, the solid filtered off, and the filtrate distilled. 1-propylthio-3-ethoxy-2-propanol was collected at 69.5-70° under 1.5 mm. pressure.

B.P.	:	69.5-70° at 1.5 mm.
Yield	:	22.5 g., 0.126 mole, 63%
n_D^{25}	:	1.4670
d_4^{25}	:	0.9850
M_D	:	50.22 (found); 50.28 (calc.)
% C	:	53.41 (found); 53.89 (calc.)
% H	:	10.49 (found); 10.18 (calc.)

g. Synthesis of 1-propylthio-3-propoxy-2-propanol

1.3 grams of metallic sodium and two moles (120 g.) of propanol-1 were placed in a 500 ml., three-necked, round-bottomed flask, equipped with thermometer, stirrer, and reflux condenser. 0.2 mole (26.5 g.) of 1-propylthio-2,3-

epoxypropane was added dropwise through the condenser and the solution stirred for one hour. It was then refluxed with stirring for three hours, cooled, and neutralized with 6N sulfuric acid. Five grams of potassium carbonate was added and the mixture allowed to stand four hours. It was then filtered and the filtrate distilled at 1.5 mm., 1-propylthio-3-propoxy-2-propanol being obtained at 81-81.5°.

B.P.	:	81-81.5° at 1.5 mm.
Yield	:	12 g., 0.06 mole, 31%
n_D^{25}	:	1.4641
d_4^{25}	:	0.9676
M_D	:	54.85 (found); 54.90 (calc.)
% C	:	56.22 (found); 56.21 (calc.)
% H	:	10.68 (found); 10.48 (calc.)

h. Synthesis of 1-propylthio-3-butoxy-2-propanol

1.3 grams of metallic sodium and 1.3 moles (100 g.) of butanol-1 were placed in a 500 ml., three-necked, round-bottomed flask, equipped with stirrer, thermometer, and reflux condenser. 0.2 mole (26.5 g.) of 1-propylthio-2,3-epoxypropane was added dropwise through the condenser and the solution stirred for one hour. It was then heated with stirring to 80° during five hours, cooled, and neutralized with 6N sulfuric acid. 100 ml. of water was added and the mixture extracted twice with ethyl ether. The combined extracts were dried over potassium carbonate, filtered and

distilled, 1-propylthio-3-butoxy-2-propanol being collected at 90.5-91° under 1.5 mm. pressure.

B.P. : 90.5-91° at 1.5 mm.

Yield : 27.5 g., 0.13 mole, 67%

n_D^{25} : 1.4639

d_4^{25} : 0.9578

M_D : 59.44 (found); 59.52 (calc.)

% C : 58.35 (found); 58.21 (calc.)

% H : 11.04 (found); 10.75 (calc.)

3. Discussion of experimental results

The methods described herein were modifications of the method of Swern, Billen, and Knight (9), using a basic catalyst to assure formation of a secondary alcohol. The yields obtained correspond to the yields obtained by the aforementioned investigators.

Figures 13, 14, and 15 indicate the variation in the refractive indices, densities, and molecular refractions of the compounds as their molecular weight varies.

4. Summary

Eight new alkylthioalkoxypropanols were synthesized and characterized.

Figure 13.

Refractive Index vs. Molecular Weight for Alkylthioalkoxypropanols of the Type $R'SCH_2CHOHCH_2OR$, R' being Ethyl or Propyl and R being Methyl through Butyl

$C_2H_5SCH_2CHOHCH_2OR$ ————

$C_3H_7SCH_2CHOHCH_2OR$ — — —

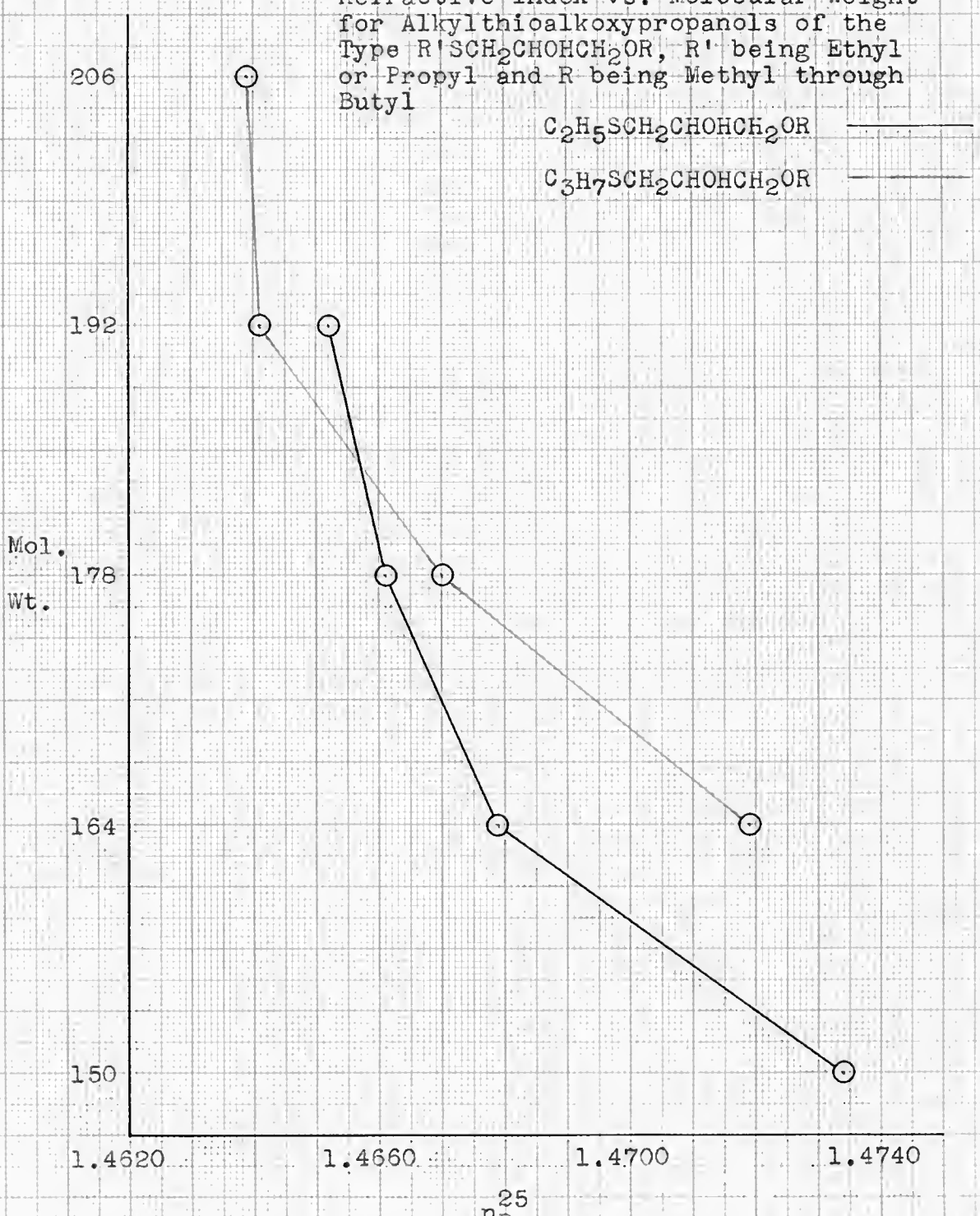


Figure 14.

Density vs. Molecular Weight for Alkylthioalkoxypropanols of the Type $R'SCH_2CHOHCH_2OR$, R' being Ethyl or Propyl and R being Methyl through Butyl

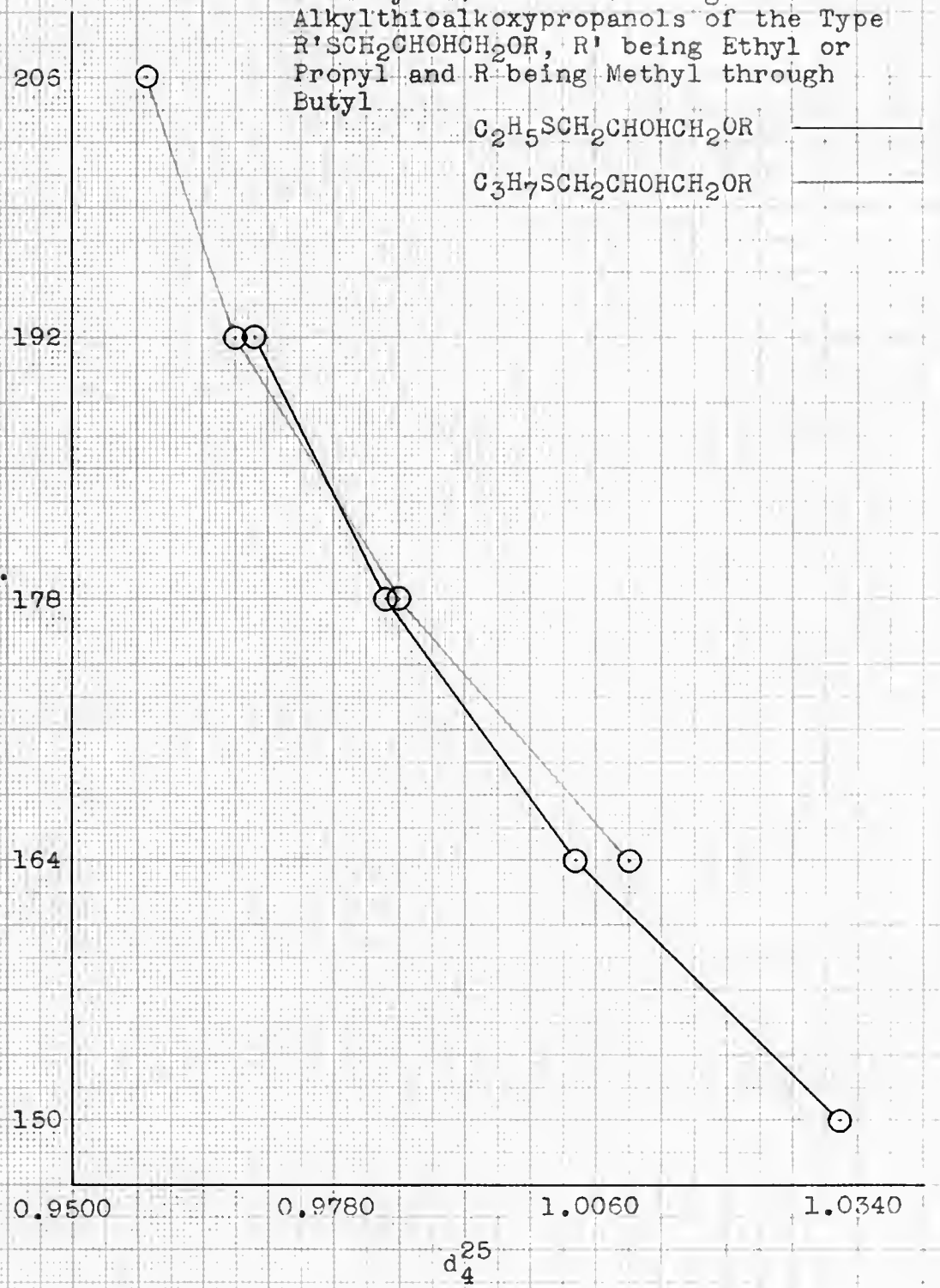
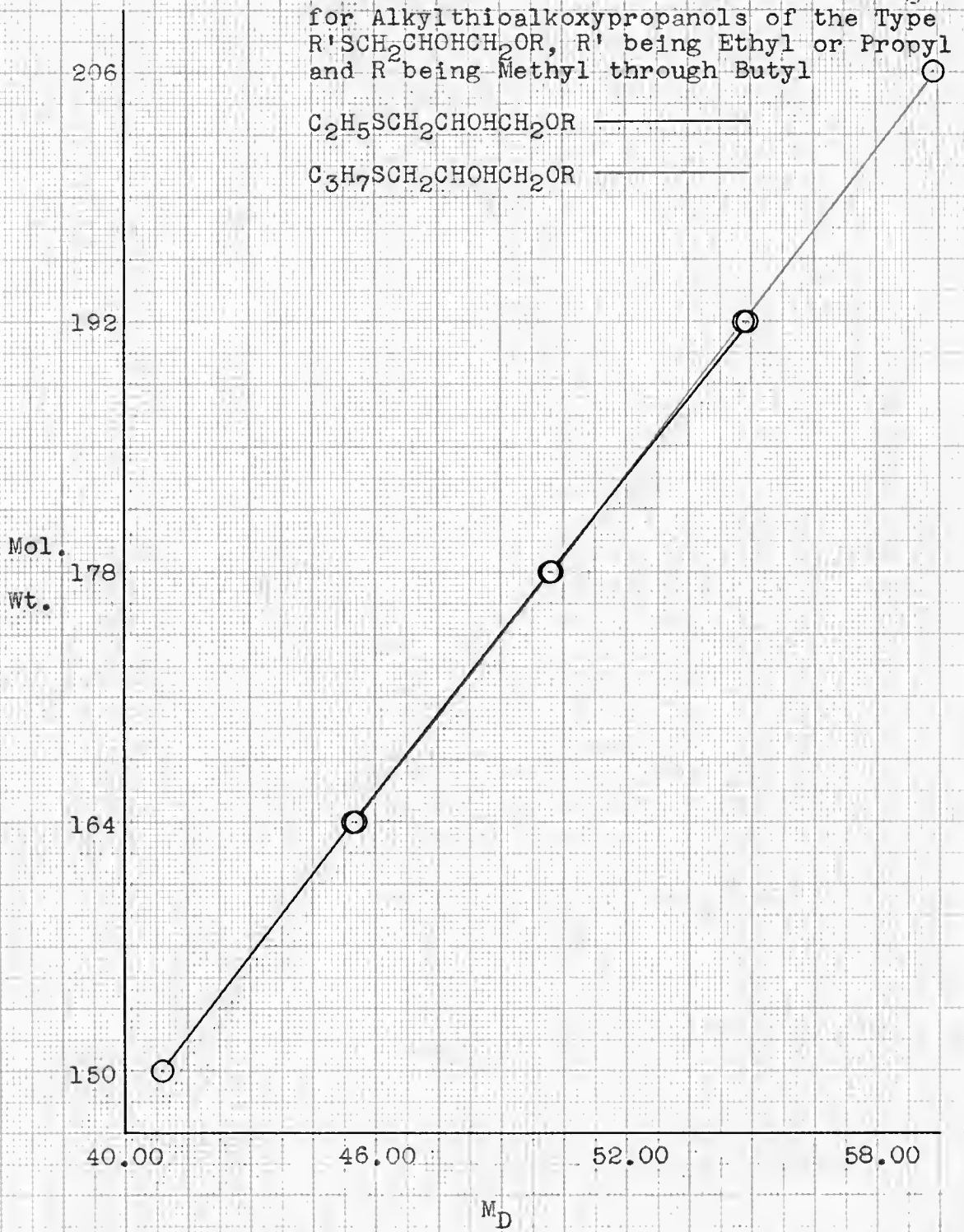


Figure 15.

Molecular Refraction vs. Molecular Weight for Alkylthioalkoxypropanols of the Type $R'SCH_2CHOHCH_2OR$, R' being Ethyl or Propyl and R being Methyl through Butyl

$C_2H_5SCH_2CHOHCH_2OR$ ——————

$C_3H_7SCH_2CHOHCH_2OR$ ——————



PROOF OF STRUCTURE

A. Of beta-hydroxypropyl sulfides and epoxypropyl sulfides

1. Review of the literature

The method of addition of compounds containing active hydrogen to unsymmetrical epoxides has long been a point of conjecture and study. It will be seen that the reaction may proceed, theoretically, in either of two directions, as illustrated by the following equations:

$$RH + R'\overline{CHCH_2O} \longrightarrow R'CH(OH)CH_2R$$

$$RH + R'\overline{CHCH_2O} \longrightarrow R'CH(R)CH_2OH$$

Krasuskii (32) showed that, when ammonia or amines reacted with unsymmetrical epoxides, the reaction conformed with the first equation. Castro and Noller (33) confirmed this observation. It has been reported by a number of investigators, working on the addition of various compounds to epoxides, that the oxirane ring was cleaved to give secondary alcohols in the presence of basic catalysts and primary alcohols in the presence of acidic catalysts (8), (9), (27), (28), (29), (30). That this is not invariably the case was shown by Swern, Billen, and Knight (9), whose work indicated that the addition of allyl alcohol to styrene oxide was just the reverse of the above generalization. The same investigators proved that the reaction of allyl alcohol with

epichlorohydrin proceeded to the secondary alcohol, regardless of catalyst.

Nenitzescu and Scarlatescu (3) reported the formation of 1-ethylthio-3-chloro-2-propanol from ethyl mercaptan and epichlorohydrin. They then prepared 1-ethylthio-2,3-epoxypropane, both by dehydrohalogenation of the ethylthiochloropropanol and by reaction of sodium ethyl mercaptide directly with epichlorohydrin, the reactions proceeding according to the equations:

$$C_2H_5SH + \overline{OCH_2CHCH_2}Cl \longrightarrow C_2H_5SCH_2CH(OH)CH_2Cl$$

$$\longrightarrow C_2H_5SCH_2\overline{CHCH_2O}$$

$$C_2H_5SNa - \overline{OCH_2CHCH_2}Cl \longrightarrow C_2H_5SCH_2\overline{CHCH_2O}$$

Fairbourne, Gibson, and Stephens (8), working on the reaction of 1,3-dichloro-2-propanol with an alcohol in the presence of base, found that the reaction proceeds in four steps, as follows:

(1) $ClCH_2CH(OH)CH_2Cl \longrightarrow ClCH_2\overline{CHCH_2O}$

(2) $ClCH_2\overline{CHCH_2O} + ROH \longrightarrow ClCH_2CH(OH)CH_2OR$

(3) $ClCH_2CH(OH)CH_2OR \longrightarrow \overline{OCH_2CHCH_2}OR$

(4) $\overline{OCH_2CHCH_2}OR + ROH \longrightarrow ROCH_2CH(OH)CH_2OR$

It is reasonable to assume that Nenitzescu and Scarlatescu's second reaction proceeded according to reactions (2) and (3) and was, therefore, no proof of the structure of the epoxy-

propyl sulfide.

Gilman and Fullhart (35) have shown that sodium methyl mercaptide reacted with styrene oxide to give $C_6H_5CH(OH)CH_2SCH_3$ by proving the latter's identity with the same compound synthesized by reduction of $C_6H_5COCH_2SCH_3$ through identity of the sulfonium iodides.

2. Experimental

a. The action of chlorohydroxysulfides on skin tissue

One drop each of the methyl, ethyl, propyl, butyl, amyl, and hexyl thiochloropropanols, prepared as shown in Section II, A, were placed on the forearm of the investigator, covered to prevent inadvertent removal, and allowed to remain overnight. Examination revealed no action whatsoever upon the skin.

b. Formation of formaldehyde from

(1) 1-ethylthio-3-chloro-2-propanol

9.5 grams of 1-ethylthio-3-chloro-2-propanol and a solution of five grams of 85% potassium hydroxide dissolved in 90 ml. of water were refluxed together for two hours. The resulting solution was made slightly acid with 6N sulfuric acid. The solution was cooled in an ice bath and five grams of potassium metaperiodate was added with vigorous stirring. After thirty minutes, the solution was filtered to remove potassium iodate and periodate, and ten ml. of the solution was distilled into 95% ethanol. The dinitrophenyl-

hydrazone of formaldehyde (m.p. 164-165°) was obtained on treatment of the alcoholic solution according to the procedure given in Shriner and Fuson (24).

(2) 1-ethylthio-2,3-epoxypropane

8.0 grams of 1-ethylthio-2,3-epoxypropane and a solution of one ml. of 98% sulfuric acid in 55 ml. of water were refluxed together for four hours. The mixture was filtered and the solution made up to 100 ml. A 50 ml. aliquot was treated with 50 ml. of 0.7337 M periodic acid solution, according to the method of Hatch and Nesbitt (37). After the chilled reaction mixture had been stirred for two hours, it was neutralized to methyl red with dilute potassium hydroxide solution, treated with a slight excess of barium chloride solution (saturated), and the precipitate of barium sulfate and barium iodate filtered off. The filtrate was made up to 250 ml. Ten ml. of this solution was analyzed for formaldehyde according to the method suggested by Walker (36). 0.2224 gram of methylene dimethone (m.p. 188-189°) was obtained, corresponding to a 60% yield of formaldehyde.

3. Discussion and summary

$$RSH + ClCH_2\overline{CHCH_2}O \longrightarrow RSCH_2CH(OH)CH_2Cl\ (I)$$

$$\longrightarrow HOCH_2CH(SR)CH_2Cl\ (II)$$

It has been shown by a number of investigators, (41), (42), (43), (44) that compounds containing chlorine beta to

a sulfide linkage, corresponding to product II above, usually exhibit a marked irritant effect on skin tissue. Since no such effect was observed in these experiments, it was deduced that the compounds tested were of type I.

$$\text{I} + \text{HOH} \longrightarrow \text{RSCH}_2\text{CH(OH)CH}_2\text{OH}$$

$$\text{II} + \text{HOH} \longrightarrow \text{HOCH}_2\text{CH(SR)CH}_2\text{OH}$$

$$\text{I} - \text{HCl} \longrightarrow \text{RSCH}_2\overline{\text{CHCH}_2\text{O}} + \text{HOH}$$

$$\text{II} - \text{HCl} \longrightarrow \overline{\text{CH}_2\text{CH(SR)CH}_2\text{O}} + \text{HOH}$$

The preceding equations show that a 1,2 glycol is formed from the hydrolysis of the chlorohydroxysulfide or epoxysulfide derived from the reaction of a mercaptan with epichlorohydrin if the reaction proceeds according to equation I, and that a 1,3 glycol results if the reaction proceeds according to equation II. It has long been known that 1,2 glycols are split to aldehydes by a solution of periodic acid while 1,3 glycols are unaffected. The reaction is discussed at length by Jackson (38). Since the hydrolysis product was split by periodic acid to give a 60% yield of formaldehyde according to the equation below, it was shown that the initial reaction between mercaptans and epichlorohydrin proceeded according to equation I.

$$\text{RSCH}_2\text{CH(OH)CH}_2\text{OH} + (\text{O}) \longrightarrow \text{RSCH}_2\text{CHO} + \text{HCHO} + \text{HOH}$$

B. Of hydroxydisulfides and hydroxydisulfones

1. Review of the literature

While it has been assumed that the reaction of epichlorohydrin with mercaptans in the presence of an excess of base leads to 1,3 disubstituted propanols (21), (22), actual proof seems entirely lacking.

2. Experimental

a. Identity of bis(butylthio)propanols

Bis(butylthio)propanol, prepared according to the procedure in Section II,C,2,d, and another bis(butylthio)propanol, prepared similarly except that potassium hydroxide rather than the acidic zinc chloride was used as a catalyst, were oxidized to disulfones with 30% hydrogen peroxide in acetic acid. The melting points of the two products and their mixed melting point were 135-136°.

b. Reaction of disulfones with sodium hydroxide

0.2501 gram of bis(ethylsulfonyl)propanol was digested with 25.00 ml. of 0.1038 N sodium hydroxide for eight hours at 80-90°. Titration of the cooled solution required 21.39 ml. of 0.1134 N hydrochloric acid. This corresponds to a 16% decomposition according to the equation,

$$RSO_2CH_2CH(OH)CH_2SO_2R + NaOH \longrightarrow$$

$$RSO_2CH_2CH(OH)CH_2OH + NaSO_2R$$

0.2456 gram of bis(hexylsulfonyl)propanol was treated in similar fashion with 25.00 ml. of sodium hydroxide solution. In this instance, 22.89 ml. of hydrochloric acid was required for neutralization. This indicates no decom-

position according to the above equation.

3. Discussion and summary

It was shown in part A of this section that the initial reaction products of mercaptans with epichlorohydrin were compounds of the types $RSCH_2CH(OH)CH_2Cl$ and $RSCH_2\overline{CHCH_2O}$. The subsequent reaction of these substances with additional mercaptan may proceed in two directions as illustrated by the following equations:

$$RSCH_2\overline{CHCH_2O} + RSH \longrightarrow RSCH_2CH(OH)CH_2SR$$

$$\longrightarrow RSCH_2CH(SR)CH_2OH$$

It was demonstrated in part 2a above that identical products were obtained with either an acidic or a basic catalyst. Oxidation of the two possible disulfides would lead to disulfones according to the equations:

$$RSCH_2CH(OH)CH_2SR \longrightarrow RSO_2CH_2CH(OH)CH_2SO_2R$$

$$RSCH_2CH(SR)CH_2OH \longrightarrow RSO_2CH_2CH(SO_2R)CH_2OH$$

It will be noted that the product in the first equation is a delta-disulfone while that in the second equation is a gamma-disulfone. It was found by Stüffer (39) that gamma-disulfones were readily decomposed by heating with dilute alkali, while beta- or delta-disulfones were unaffected. Subsequently, Otto and Tröger (40) found that an additional reaction occurred. These two reactions are outlined by the following equations:

$$RSO_2CH_2CH_2SO_2R + NaOH \longrightarrow RSO_2CH_2CH_2OH + NaSO_2R$$

$$RSO_2CH_2CH_2OH + RSO_2CH_2CH_2SO_2R + NaOH \longrightarrow$$

$$RSO_2CH_2CH_2OCH_2CH_2SO_2R + NaSO_2R + H_2O$$

The conditions for the decomposition as used in part 2b above were those of Stüffer. Little or no reaction was observed where Stüffer reported complete decomposition under these conditions. It was thus proved that the sulfones synthesized were delta-disulfones rather than gamma-disulfones.

The small amount of decomposition of the diethyl disulfone may possibly be accounted for by the etherification reaction of Otto and Tröger since the required hydroxy group was present in the initial compound.

Thus, it has been shown that a delta-disulfide (or a secondary alcohol) rather than a gamma-disulfide (or a primary alcohol) was formed when an epoxypropyl sulfide reacted with a mercaptan.

SUMMARY

The condensation of epichlorohydrin (1-chloro-2,3-epoxypropane) with normal mercaptans, methyl through hexyl, to form chlorohydroxypropyl sulfides ($RSCH_2CHOHCH_2Cl$) was investigated.

The chlorohydroxy propyl sulfides were oxidized to sulfones ($RSO_2CH_2CHOHCH_2Cl$).

By dehydrohalogenation, corresponding series of epoxypropyl sulfides and epoxypropyl sulfones were formed from the chlorohydroxypropyl sulfides and chlorohydroxypropyl sulfones, respectively. The epoxypropyl sulfones are a new class of compounds.

Six bis(alkylthio)propanols ($RSCH_2CHOHCH_2SR$) where R was methyl through hexyl, resulted from the addition of mercaptans to epoxysulfides or epichlorohydrin. These compounds were oxidized to a series of bis(alkylsulfonyl)propanols ($RSO_2CH_2CHOHCH_2SO_2R$).

Eight new alkylthioalkoxypropanols were obtained through the combination of epoxypropyl sulfides with alcohols.

The structures of the chlorohydroxypropyl sulfides, the epoxypropyl sulfides, and the bis(alkylthio)propanols were proven by several methods.

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BIOGRAPHY

Thomas K. Todsen was born in Pittsfield, Massachusetts, on October 21, 1918, but moved to St. Petersburg, Florida at an early age.

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During his graduate career, Todsen has held the Tennessee Corporation Research Fellowship and the Dudley Beaumont Memorial Fellowship. He has also served as teaching assistant and interim instructor (part-time) in chemistry.

COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfillment of the requirements of the degree of Doctor of Philosophy.

Date September 2, 1950

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